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THE ROLE OF ENDORPHINS IN THE PATHOPHYSIOLOGY
OF HEMORRHAGIC AND ENDOTOXIC SHOCK IN
THE SUBHUMAN PRIMATE

Annual and Final Report

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In order to investigate the pathophysiological role of endogenous morphine-like substances (endorphins) in shock, we studied cynomolgus monkeys and dogs subjected to hemorrhagic or endotoxic shock. Blockade of opiate receptors with naloxone improved cardiovascular function and survival in both species and both models but requires correction of acidosis and hypothermia. Shock is associated with elevations in plasma levels of endorphins. Using different sites of injection, and various anatomical and pharmacological ablations, we have shown that naloxone's beneficial effects in hemorrhagic shock are due to potentiation of the effect of released catecholamines on cardiac opiate receptors. The myocardial depression found in shock is due to an endorphin-mediated attenuation of catecholamine activity on the heart. We believe this is mediated by interaction with cardiac receptors and is expressed via G-protein activation of adenylate cyclase and cyclic-AMP. This hypothesis needs to be tested by biochemical determination of these substances, and our observations need to be extended to endotoxic shock. Nevertheless, naloxone and other

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SUMMARY

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FOREWORD

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals", prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, revised 1978).

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BODY OF REPORT

a)   Problem and Background

        Shock due to hemorrhage, trauma, and sepsis remains an impor-
tant threat to the health and welfare of the soldier in war. Even
during peacetime, septic and hypovolemic shock are frequent and impor-
tant causes of morbidity and mortality in the civilian and military
populations. These shock states do not always respond to appropriate
therapies suggesting the involvement of other pathophysiological mecha-
nisms and hence other treatment options. The exigencies of the battle-
field situation and the availability of rapid evacuation make the use of
simple, rapid, on-the-scene anti-shock therapies highly desirable.

        Endogenous morphine-like substances (endorphins) are elevated
in the plasma in response to stress (1). Endogenous and exogenous
opiates depress the cardiovascular system when given intravenously or
into the central nervous system (2). The possible involvement of
endorphins in the pathophysiology of shock was initially evaluated by
Holaday and Faden using rodent models of hemorrhagic and endotoxic
shock. Opiate receptor blockade with naloxone improved mean arterial
pressure and pulse pressure in rats after hypovolemic hemorrhage (3) or
the injection of endotoxin to induce shock (4). This was associated
with increased survival in hemorrhage but not in endotoxemia. Subse-
quently, we showed increased mean arterial pressure, cardiac output and
myocardial contractility in canine hemorrhagic (5) and endotoxic shock
(6). We also demonstrated improved survival; naloxone converted a 100%
lethal hemorrhagic model to 100% survival and an 80% lethal endotoxic
shock model to 30% survival.

These results were then extended to humans by others and reported as letters to the editor (7) or uncontrolled, non-randomized trials (8,9). A very recent randomized trial showed no benefit to the use of naloxone in human septic shock (10), but the doses of naloxone used were quite low compared to those found to be effective in rodents, dogs (3-6) and monkeys (vide infra). We chose, instead, to study the doses required, the efficacy, and any side effects of naloxone in a subhuman primate, the cynomolgus monkey. Primates are closer to man than other species studied, and their responses would be better to study before extensive human use. Once we established effectiveness and dosages, we investigated mechanisms using dogs because of the number of animals required.

b) Approach

Cynomolgus monkeys or dogs were lightly anesthetized and instrumented to measure mean arterial pressure (MAP), cardiac output (CO), heart rate (HR), pulmonary arterial pressures, and myocardial contractility (LV dp/dt max). Shock was induced by the intravenous injection of E. coli endotoxin or by bleeding into a reservoir to achieve and maintain MAP at 45 mmHg. The animals were treated i.v. with either naloxone 2 mg/kg bolus plus 2 mg/kg·hr infusion for 4 hours or 0.9% NaCl in equivalent volumes when MAP reached 75 mmHg in endotoxemia or after 1 hr of hemorrhage (MAP 45 mmHg). Shed blood was reinfused 1 hr later in the hemorrhage model. These experiments (or slight modifications thereof) were also done after pharmacological or surgical ablation of various components of the neurohumoral responses to shock. Naloxone was also given directly into the central nervous system or the coronary artery to sort out central nervous system from peripheral

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cardiac actions. Stereoisomers of naloxone, other opiate receptor antagonists like naltrexone and nalbuphine, and other anti-endorphin substances (namely TRH) were also used.

c)   Results: Endotoxemia in monkeys (n=12)

Naloxone significantly increased MAP by 25-30 mmHg over saline treated controls (p<.02 by analysis of variance, ANOVA, Figure 1). Left ventricular contractility was higher in naloxone treated monkeys (3.6 x 10^3 mmHg/sec) than in controls (2.4 x 10^3 mmHg/sec, p<.01 by ANOVA). Naloxone improved LV dp/dt max by 800 mmHg/sec compared to no change with saline (p<.02 by ANOVA, Figure 2). There were no differences between naloxone and saline treatment in CO, stroke volume, HP, peripheral vascular resistance, temperature or metabolic measurements. All of the naloxone-treated animals were alive at 48 hours but only 1/6 saline treated controls (p<.05 by Fisher's exact test). Plasma levels of ꞵ-endorphin and its precursor ꞵ-lipotropin rose 4-5-fold and were not affected by treatment (Table I).

d)   Results: Hemorrhage in monkeys (n=22)

In the first group of 10 monkeys we could not find a difference in cardiovascular responses between naloxone and saline treatment (Figures 3 and 4). We noted that the naloxone treated animals were acidotic (Figure 5) and colder (Figure 6) than saline-treated animals before treatment. Furthermore, analysis of the MAP responses (as a pressure time product) showed that these responses were affected by temperature and acid-base balance. Acidosis attenuated the pressure x time product in response to naloxone (Figure 7); cold attenuated the plasma ꞵ-endorphin response to stress (Figure 8) and the pressure x time product in response to naloxone (Figure 9).

When acidosis and hypothermia were treated or prevented, the monkeys responded to naloxone (n=6) with significant increases in MAP (Figure 10) and LV dp/dt max (Figure 11) compared to no response to saline (n=6). This response increased survival with 5/6 naloxone-treated monkeys alive at 24 hr versus 2/6 saline-treated controls (p<.05). The one naloxone-treated monkey that did not survive at 24 hrs had an iatrogenic death due to a left ventricular catheter-induced myocardial injury. Plasma β-endorphin and β-lipotropin rose 4-5-fold (Table II) and were uninfluenced by treatment. Whole blood histamine levels were unaffected by shock (Table III).

e) Results: Central nervous system injections

Injection of an enkephalin analogue D-ala^2-met^5-enkephalinamide (DAME) into the IIIrd ventricle of conscious monkeys produced *bradycardia and hypotension* (Figure 12) which were dose-dependent and attenuated by naloxone (Figure 13). Microinjection of DAME into stereotactically implanted areas from the diencephalon to the medulla in normotensive unanesthetized monkeys reduced blood pressure and (inconsistently) heart rate. Injection of naloxone into these DAME-sensitive sites when the animals were anesthetized and subjected to hypovolemic shock, however, failed to increase blood pressure by more than 5 mmHg (Table IV).

f) Results: Corticosteroid-naloxone interactions (n=77)

Dexamethasone and methylprednisolone are putatively beneficial in canine hemorrhagic shock (11). However, these steroids at their maximally effective dosages were not as effective as naloxone when given in our canine hemorrhagic shock model. Indeed, dexamethasone or methyl-prednisolone at maximally effective doses actually decreased the

beneficial effects of naloxone on hemodynamics and survival. This was true whether blood was returned to the animal (Figure 14) or not (Figures 15 and 16). These steroids were slightly beneficial but not nearly so as naloxone. We postulated that large doses of these steroids were preventing endorphin release. Hence, naloxone, having less endorphin to block, would appear to be less effective.

g)   Results: Adrenalectomy (n=23)

Since corticosteroids seemed to have an important interaction with naloxone and because the adrenal contains endorphins, we treated dogs with naloxone or saline one week after adrenalectomy when their plasma endorphin levels were quite high (due to loss of negative feedback by corticosteroids on the pituitary release of ß-endorphin). We expected to find enhanced responses to naloxone because of the high plasma endorphin levels. Adrenalectomy, however, completely abolished the MAP and CO responses and markedly attenuated the LV dp/dt max response to naloxone. The full naloxone response could be restored by physiological doses of hydrocortisone 45 minutes before naloxone (Figures 17-19). The adrenal would not appear to be the source of endorphins producing cardiovascular depression in shock. Moreover, naloxone's effectiveness in shock requires an intact adrenal; the factor lost by adrenalectomy appears to be adrenocortical since corticosteroid restore naloxone's effectiveness. Cortisol is required for production (12), stability (13), and receptor binding (14) of catecholamines. Therefore, we thought that there was an endorphin-catecholamine interaction in the peripheral vasculature or the heart which resulted in depression during hemorrhagic shock which was unmasked by naloxone. This idea led to the following series of experiments in dogs.

h)   Results: Autonomic nervous system involvement

        Naloxone causes a transient decrease in HR and sustained
increases in MAP, CO, and LV dp/dt max in canine hemorrhage. The role
of the autonomic nervous system was investigated by means of cardiac
denervation and pharmacological blockade (n=50). The transient
bradycardia was prevented by β-adrenergic receptor blockade or cardiac
denervation. The sustained hemodynamic responses were unaffected by
cardiac denervation (Figure 20). They were, however, attenuated
significantly by either α- or β-adrenergic blockade (phenoxybenzamine or
metoprolol, respectively) and potentiated by cholinergic receptor
blockade with methylatropine (Figure 21). In these and most subsequent
figures, the results are shown as the mean net naloxone effect which is
the difference over 30 minutes between the mean response to naloxone and
the mean response to saline. Cardiac denervated dogs experienced a
tachycardia in response to naloxone which was blocked by β-adrenergic
blockade with metoprolol. Naloxone had no effect on plasma
catecholamine levels (Table V). The sustained cardiovascular responses
to naloxone were the result of a parasympathetic stimulation which
modestly attenuated an adrenergic component. The adrenergic stimulation
of the heart after naloxone appeared to result from existing adrenergic
stimulation and not sympathoadrenal discharge.

        We tested the hypothesis that naloxone potentiated the effects
of neurally and adrenally released catecholamines (n=60). Catecholamine
release was attenuated by a combination of surgical adrenal denervation
and pharmacological ganglionic blockade with chlorisondamine (Table VI).
Adrenal denervation or chlorisondamine alone attenuated the
cardiovascular responses to naloxone in hemorrhage. Denervation and

chlorisondamine in combination completely blocked the mean net naloxone
effect which could be completely restored by infusion α- and
β-adrenergic agonists at a constant rate prior to naloxone treatment
(Figure 22).

We thought that naloxone's potentiation of released catechola-
mines was primarily on the heart. Naloxone or its inactive stereoisomer
were given intravenously (i.v.) or directly into the coronary artery
(i.c.) in dogs anesthetized and subjected to hemorrhagic shock.
Naloxone 2 mg/kg i.v. or 0.2 mg/kg i.c. significantly improved MAP, CO,
and LV dp/dt (Figure 23). Saline or naloxone 0.2 mg/kg i.v. were
without beneficial effects. The hemodynamic responses to naloxone i.c.
were dose-dependent and stereospecific. We concluded that naloxone's
beneficial effects in canine hemorrhagic shock were due to its action at
stereospecific cardiac opiate receptors.

We repeated some of these crucial experiments in monkeys
(n=20). Ablation of catecholamine responses by adrenalectomy and
chlorisondamine completely prevented the increase in MAP and LV dp/dt
max due to naloxone in hemorrhage. The usual response to naloxone was
restored by infusion of α- and β-adrenergic agonists (Figures 24 and
25).

i) Results: Blood flow

Normovolemic (n=10) and hypovolemic (n=10) dogs were given
either saline or naloxone. Naloxone had no effect on the regional blood
flow distribution as measured by microspheres in normovolemia. In
contrast, naloxone significantly increased blood flow to the heart,
intestine, liver (arterial) and adrenal glands when given during

hypovolemic shock (Table VII).These results show increased perfusion of vital organs as a result of improved cardiac action.

j)   Results: Naltrexone, nalbuphine, and TRH

We also investigated the use of other agents in shock. The longer acting opiate receptor antagonist naltrexone also improves cardiovascular hemodynamics and survival in canine hemorrhagic shock (Figures 26-29). These results are dose-dependent and support the view that opiate-receptors and/or endorphins are involved in the shock-induced cardiovascular depression by satisfying one of the criteria for opiate involvement (15), namely effectiveness of another opiate antagonist. Naloxone potentially might increase pain perception so we investigated the effectiveness of thyrotropin-releasing hormone (TRH) in primate shock. TRH is a physiological antiendorphin with effects opposite to those of the endorphins without affecting pain perception or binding to opiate receptors (16,17). TRH increases MAP and LV dp/dt max in primate hemorrhagic (Figures 30 and 31) and endotoxemic shock (Figures 32 and 33). These cardiovascular responses were associated with increased survival in hemorrhage but not endotoxemia. The mixed opiate receptor agonist/antagonist nalbuphine relieves pain and yet reverses the cardiovascular depression in canine hemorrhagic shock (Figures 26-29). Survival was also improved These canine studies were done for a private contractor. However, primate studies done under our Army Contract showed no improvement in hemodynamics or survival.

k)   Results: Importance of timing

Delay in naloxone treatment (n=9, versus saline controls n=9) by only 30 min in canine hemorrhage resulted in more modest increases in

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MAP (Figure 34), CO (Figure 35), LV dP/dt max (Figure 36) and survival than usual (5). On the other hand, in experiments not covered by this contract, naloxone pre-treatment had some unique effects on endotoxin-induced cardiovascular effects and pathology: it prevented the typical bloody diarrhea, maintained superior mesenteric arterial blood flow and blunted the pulmonary arterial and portal venous hypertensive responses. Survival was also increased to a similar extent (LD_{80} to LD_{20}) as when naloxone was given 15 min after endotoxin without affecting bloody diarrhea or these cardiovascular parameters (6).

1) Results: Other studies on mechanisms and sites of action

Catheters were placed into the central nervous system of dogs. Naloxone (n=5) perfused intracerebroventricularly at 0.1 mg/kg failed to improve MAP (Figure 38), CO (Figure 39) or LV dP/dt max (Figure 40) compared to artificial CSF (n=5) in canine hemorrhage. In contrast, this same dose and route of administration of naloxone (n=5) increased these cardiovascular parameters (Figures 41-43) significantly compared to artificial CSF (n=5) in canine endotoxic shock. Naloxone (n=5) given intrathecally into the cisterna magna failed to have significant cardio-vascular effects compared to CSF alone (n=5) in our canine hemorrhagic shock model (Figures 44-46).

The exogenous opioid morphine depresses cardiac function in a dose-dependent and naloxone reversible way (18). A portion of this cardiovascular depression involved histamine release because it was blocked by antihistamines working at the H_1 and H_2 receptors. There were also some direct cardiac depressant effects independent of histamine release which were identified using cardiopulmonary bypass in dogs to separate cardiac and peripheral vascular effects (19).

Opiates failed to release histamine when injected into the intact rat or following incubation with rat peritoneal mast cells, a rich source of histamine. On the other hand, opiates did increase plasma levels of epinephrine and norepinephrine three- to fivefold which was naloxone-blockable and -reversible (19).

m)   Discussion

Naloxone improves cardiovascular function and survival in canine and primate hemorrhagic and endotoxemic shock. Our results in primate shock indicate its possible usefulness in human shock but at much higher doses than have been previously reported (in letters to the editor) (reviewed in 7) to be beneficial in human septic or cardiogenic shock. In two uncontrolled, nonrandomized trials naloxone was shown to be effective when given to humans in shock (8,9). These two articles differ in the doses of naloxone used with neither one achieving the dosages we have found to be maximally effective in our primate models. The two studies also differed in that steroids were shown to have no effect by Groeger (9) and a detrimental effect on the hemodynamic response to naloxone by Peters (8). The latter observation would be more consistent with our observations. However, some steroid is necessary for the full naloxone response. Hence some of Peters' "adrenocorticopenic patients" may not have responded because they had had hypophysectomy whereas others in this group merely had received large doses of corticosteroid. Groeger also showed that delay in treatment decreases the effectiveness of naloxone which agrees with our results and those of others (20).

The most recent publication on the human use of naloxone (10) shows no significant cardiovascular effects with doses of naloxone with

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which we would not have found an effect in monkeys. These authors also failed to note body temperature and acid-base balance, which we have shown clearly to be important in the naloxone response. After our initial report (21), others have shown that ambient and body temperature are important determinants of the naloxone response in canine endotoxemia (22) and hemorrhagic shock (23) respectively. We would maintain that the ambient temperature effect is mediated by a response in body temperature based upon our results as well as inspection of these authors' results (22).

Our pharmacological and surgical dissection of the naloxone response points to a peripheral cardiac opiate receptor site of cardio-vascular depression in canine hemorrhagic shock and its reversal by naloxone. Naloxone appears to potentiate existing adrenergic stimuli at the heart by unmasking endorphin mediated depression. A unifying hypothesis would be an endorphin-catecholamine interaction at the cardiac ß-adrenergic receptor and G-proteins. Such an interaction has been demonstrated for morphine and prostaglandins in vivo and in vitro. It is manifested through G-protein activation of adenylate cyclase with biochemical expression through cyclic AMP (Figure 47). Cyclic-AMP then phosphorylates key proteins important to intracellular calcium metabol-ism and myocardial excitation-relaxation coupling (and ultimately myocardial contractility). These ideas are shown in Figure 48 with known components indicated by asterisks. Such biochemical correlations of physiological interactions are presently being explored in our laboratory. Endorphins elevated in shock attenuate beneficial cate-cholamine effects and this attenuation is unmasked by naloxone. This supersensitivity to catecholamines may explain some of the side-effects

of naloxone, especially hypertension (24) and arrhythmias (25).

Naloxone may also increase catecholamine release in certain situations,

and this result should dictate extreme care in its clinical use.

Endotoxic shock appears to involve different naloxone-

sensitive mechanisms than hemorrhagic shock. Endotoxemia results in a

depression in central sympathetic nerve activity as measured in

splanchnic nerves. Naloxone reverses this depression and enhances

activity in the splanchnic nerves (26). Central nervous system

injection of naloxone has been shown to improve cardiovascular

parameters which are then lost in hypophysectomized rats subjected to

endotoxemia (27) or hemorrhage (28). However, adrenal atrophy may have

resulted due to hypophysectomy and prevented the naloxone response.

Others have shown that intracerebroventricular perfusion of naloxone

prevents endotoxin-induced decreases in cardiovascular function (29).

We have shown that intracerebroventricular perfusion of naloxone fails

to increase MAP, CO, or LV dp/dt max in canine hemorrhagic shock but

does improve these cardiovascular parameters in endotoxemic shock.

Intrathecally administered naloxone similarly fails to improve

cardiovascular function in canine hemorrhage. These results in toto

would be consistent with different sites for naloxone's effectiveness in

hemorrhage and endotoxemia, peripheral cardiac in the former and central

nervous system in the latter. By analogy, these sites are also where

endorphins depress cardiovascular function in these respective shock

paradigms. We need to investigate endotoxemic shock pharmacologically

and surgically like we did hemorrhagic shock to exclude possible overlap

in mechanisms.

Naloxone appears to be a safe and beneficial agent in the treatment of shock. Other agents like naltrexone, nalbuphine and TRH are available and seem to be effective. Their theoretical advantages have not clearly been established.

n) Conclusions

1. Naloxone improves mean arterial pressure, cardiac output, myocardial contractility, and survival in canine and primate endotoxic and hemorrhagic shock.

2. The site of cardiovascular depression by opiates and its reversal by naloxone appears to be at stereospecific opiate receptors on the heart in hemorrhage. Naloxone potentiates the effects of existent catecholamine activity on the heart by blocking endorphin attenuation of the adrenergic effect.

3. Naltrexone, nalbuphine and TRH are also effective anti-endorphin substances in shock.

o) Recommendations

1. Continue to pursue controlled randomized clinical trials of naloxone in human shock.

2. Investigate the biochemical correlations predicted by our hypothesis, i.e., adenylate cyclase and cyclic-AMP activity in the heart subject to catecholamines and opiates in various combinations.

3. Investigation of mechanisms of cardiovascular depression by opiates in endotoxemic shock by direct intracoronary injection of naloxone and by adrenalectomy and ganglionic blockade followed by infusion of - and -adrenergic agonists.

Table I: Plasma ɑ-endorphin (β-EP) and b-lipotropin (ɑ-LPH) in monkey endotoxemia as measured by radioimmunoassay (values in pg/ml)

	Group	Baseline	Treatment=T	T+30 min	End
β-EP	Saline	201±99	521±118	781±142	450±107
	Naloxone	170±93	605±118	936±203	479±100
β-LPH	Saline	28±28	373±166	844±293	450±154
	Naloxone	131±131	685±292	972±428	453±219

Table II: Plasma ɑ-endorphin (β-EP) and β-lipotropin (β-LPH) in monkey hemorrhage shock as measured by radioimmunoassay (values in pg/ml)

	Group	Baseline	0	60	90	300
β-EP	Saline	382±125	1072±187	1171±265	1289±122	583±228
	Naloxone	230±64	661±47	895±142	988±164	476±82
β-LPH	Saline	396±164	1374±364	674±168	1936±498	790±249
	Naloxone	108±42	617±133	798±246	2316±1193	615±213

Table III: Whole blood histamine in monkey hemorrhagic shock as measured by radioenzymatic assay (results in ng/ml)

| Group | Time, min | | | | | |
	-60	0	60	120	180	210
Experimental	13±2	17±2	15±5	16±3	25±6	33±6
Normal literature value 19±9						

Table IV: Effects of intracerebral infusion of naloxone (nal) into multiple opioid-sensitive sites on mean arterial pressure (MAP) during primate hemorrhagic shock

| Animal | Total nal in 60', nm | MAP (mmHg) | | | Survival |
		Control	Post-hem	Max Δ	
1	0.587	96	45	+20	+
2	0.176	100	45	+ 5	+
3	1.121	108	45	+12	—
4	0.856	100	45	0	—
5	1.835	100	45	+ 5	—
6	0.920	50	45	+16	—

Table V: Effect of surgical and pharmacological autonomic intervention on plasma catecholamines in canine hemorrhagic shock as measured by radioenzymatic assay (baseline values in pg/ml, rest in mcg/ml)

Intervention	Time	Treatment	Epinephrine	Norepinephrine	Dopamine
Surgical	Baseline		68±35	234±41	114±48
	Shock		18.9±3.4	6.5±0.9	1.6±0.3
	+30 min	Saline	26.5±10.7	8.0±0.7	2.2±0.2
		Naloxone	15.8±2.6	7.9±2.4	1.8±0.4
Pharmacological	Baseline		58±8	213±134	57±50
	Shock	Saline	19.3±3.7	8.6±2.8	1.4±0.2
		Metoprolol	21.1±7.0	5.2±1.3	1.0±0.2
		Phenoxy-benzamine	9.4±1.5	4.2±0.5	1.0±0.2
		Both	14.1±3.5	9.7±4.2	1.1±0.3
		Methylatro-pine	15.6±3.7	2.9±0.3	0.2±0.7

Table VI: Effect of adrenal denervation (AD) and ganglionic blockade with chlorisondamine (CHL) on plasma catecholamines in canine hemorrhagic shock (baseline values in pg/ml, rest in mcg/ml; also as % of sham AD post-hemorrhage in parentheses)

Group	Epinephrine	Norepinephrine	Dopamine
Sham AD baseline	274±236	180±48	45±29
Post-hemorrhage	18.8±3.8 (100%)	4.2±0.6 (100%)	0.8±0.1 (100%)
AD	2.3±0.2 (12%)	1.2±0.2 (30%)	0.15±0.03 (18%)
CHL	2.1±0.9 (11%)	0.9±0.2 (22%)	0.14±0.02 (19%)
AD+CHL	0.14±0.06 (1%)	0.49±0.06 (12%)	0.04±0.02 (4%)

Table VII: Regional blood flow distribution (ml/min/100 gm) during
hemorrhage hypotension in the dog

	Baseline	Shock	Change after Treatment with		
			Saline	Naloxone	p
Heart	169±14	128±19	24±25	118±18	.015
Adrenal	356±41	196±28	-24±55	283±47	.003
Intestine	117±21	29±5	-13±7	15±5	.012
Liver	33±13	16±3	-5±6	18±5	.011
Kidney	865±66	135±18	-2±53	102±53	.204
Brain	81±8	64±8	-7±7	3±5	.257

PRIMATE ENDOTOXIN SHOCK

o—o TREATED 2 mg/kg naloxone
▲—▲ CONTROL 0.9 % NaCl
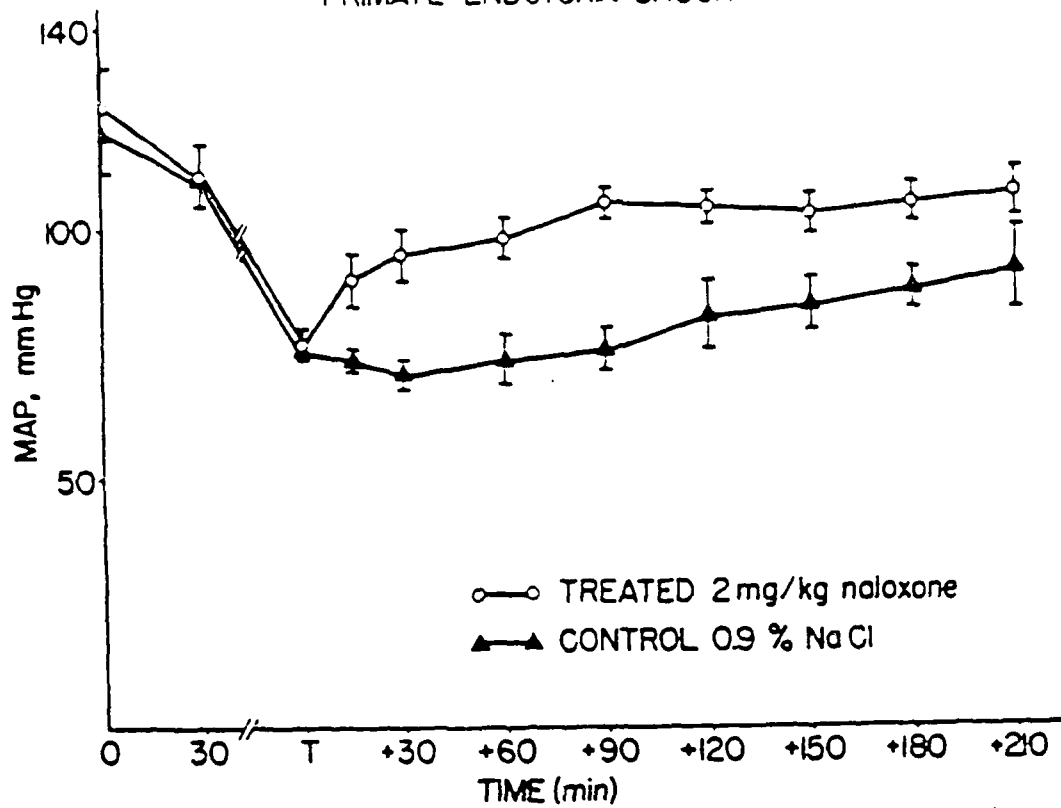
Figure 1

PRIMATE ENDOTOXIN SHOCK

o—o TREATED
2 mg/ml naloxone
▲—▲ CONTROL
0.9 % NaCl
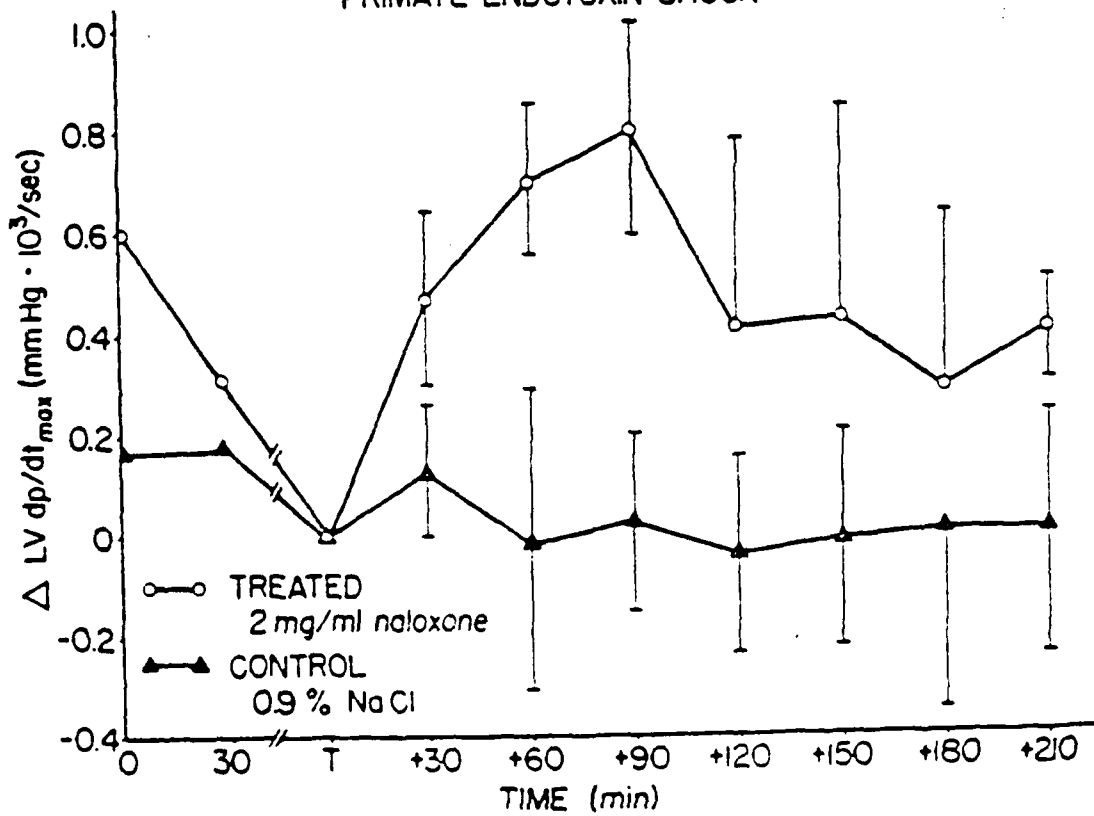
Figure 2

PRIMATE HEMORRHAGIC SHOCK
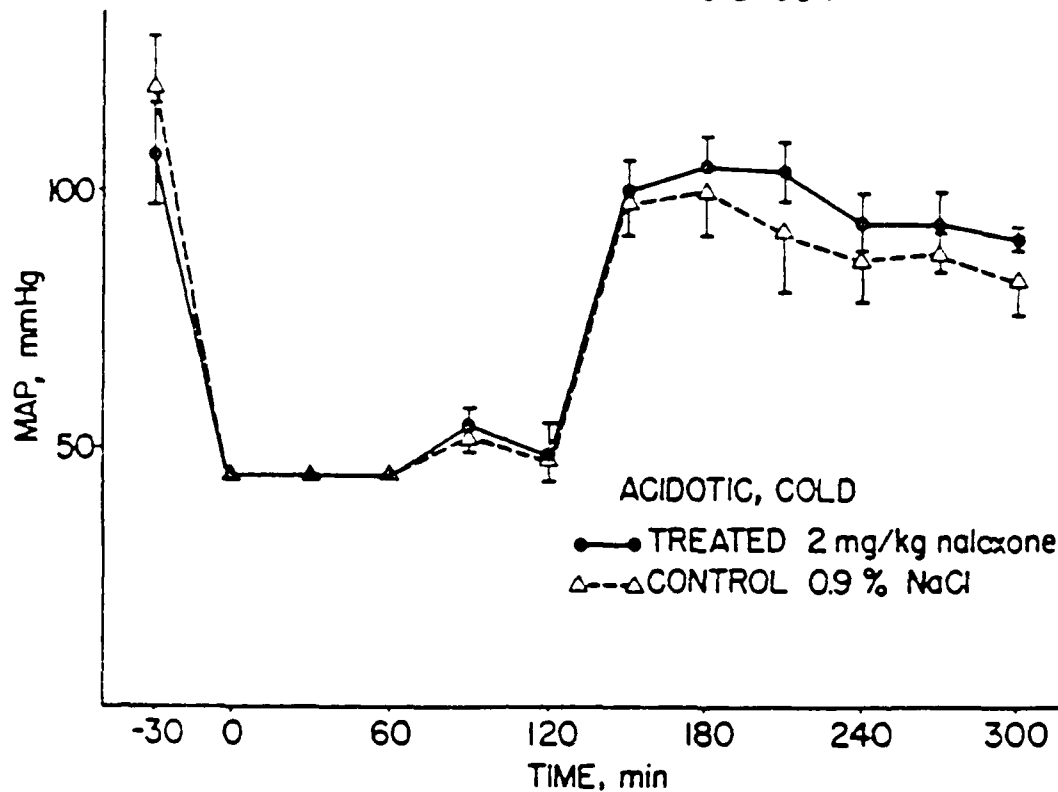
Figure 3

PRIMATE HEMORRHAGIC SHOCK

Figure 4

PRIMATE HEMORRHAGIC SHOCK
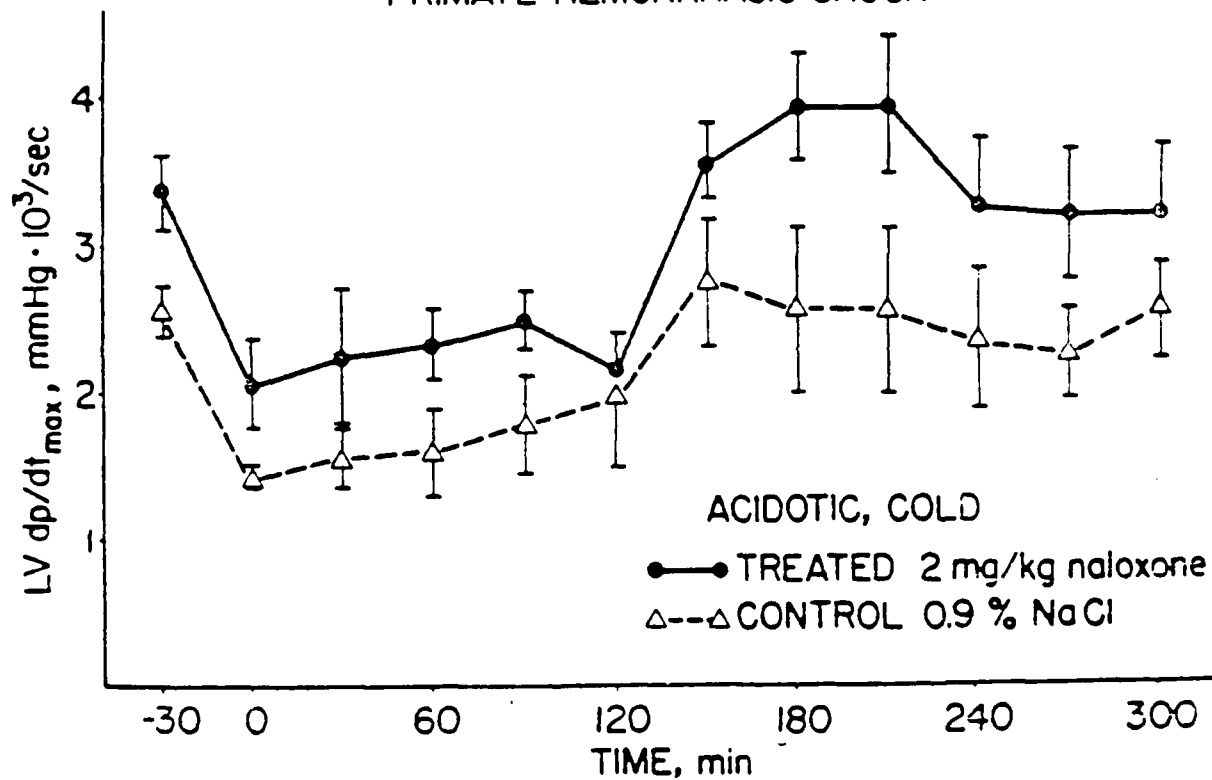
Figure 5
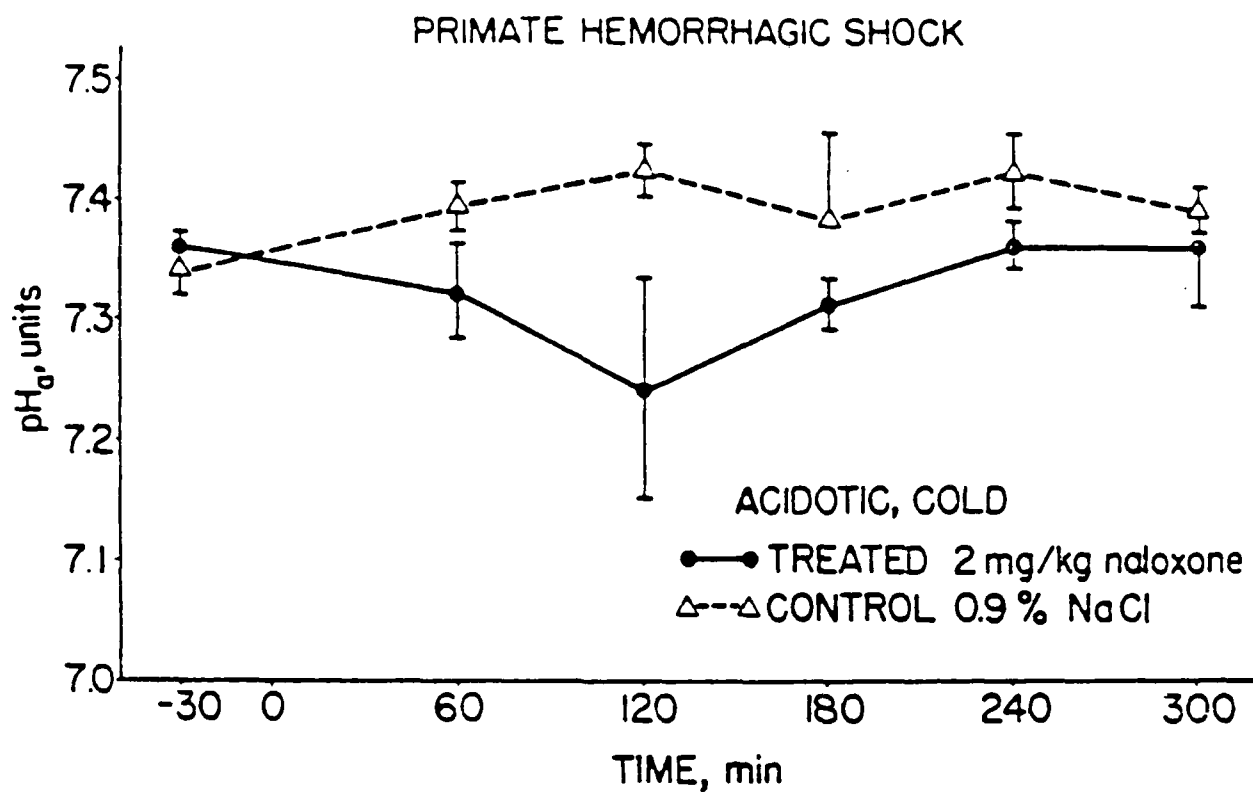
PRIMATE HEMORRHAGIC SHOCK
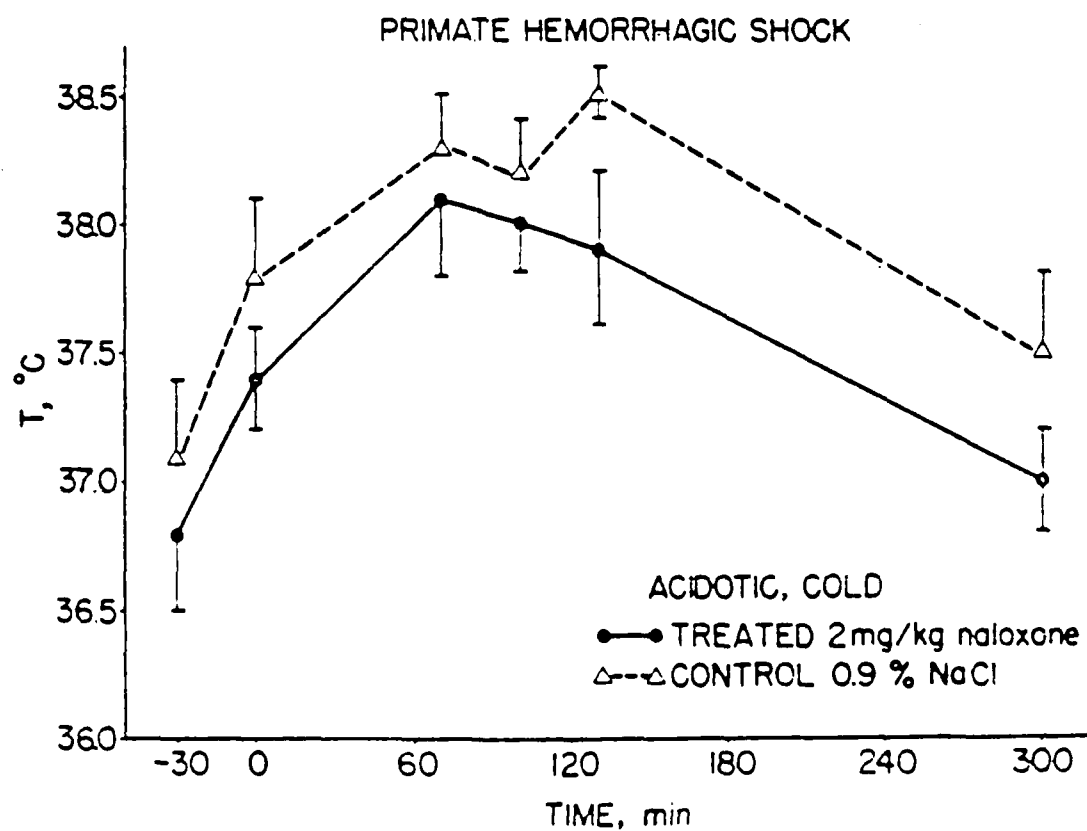
Figure 6

PRIMATE HEMORRHAGIC SHOCK

AREA SCORE=1774(pH$_a$-7.0)-19
r=0.98, p<0.01

F(1,3)=20.07
p<0.05 BY ANOVA

ACIDOTIC, COLD
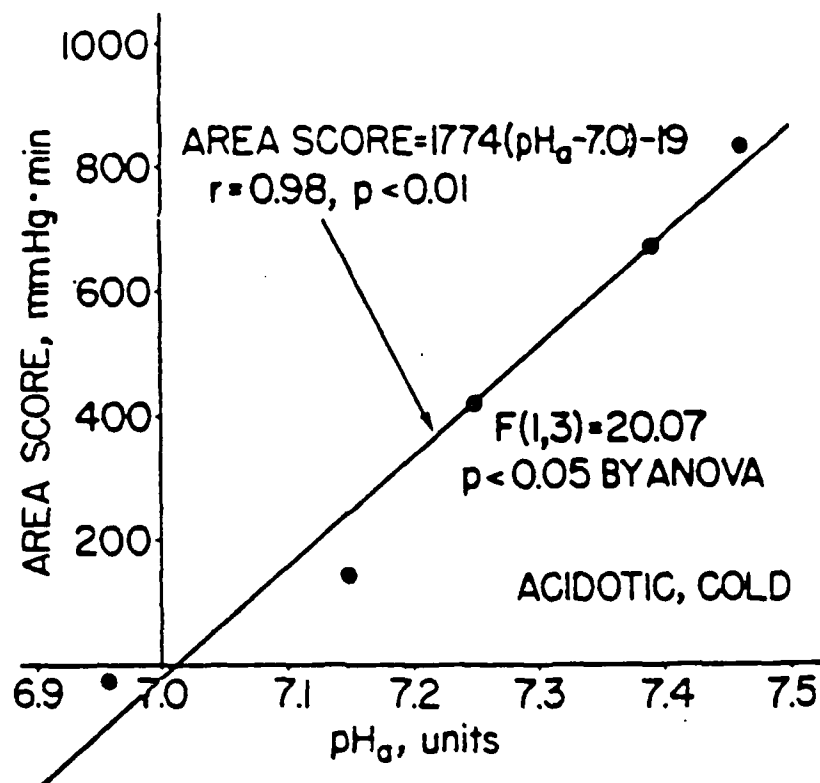
Figure 7

PRIMATE HEMORRHAGIC SHOCK

β-END=334(T-37.0)+597
r=0.67, p<0.05

ACIDOTIC, COLD

Figure 8

-27-
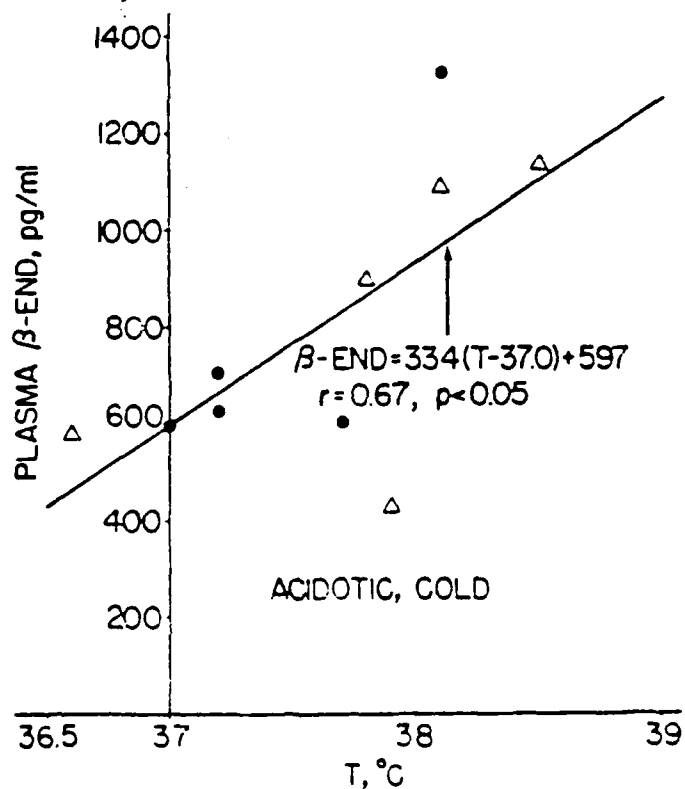
PRIMATE HEMMORHAGIC SHOCK

AREA SCORE = 648(T-37)-180
r=0.75

ACIDOTIC, COLD

Figure 9

PRIMATE HEMORRHAGIC SHOCK

TREATED 2 mg/kg naloxone
CONTROL 0.9 % NaCl

Figure 10

PRIMATE HEMORRHAGIC SHOCK

TREATED 2 mg/kg naloxone
CONTROL 0.9 % NaCl

Figure 11

-33-
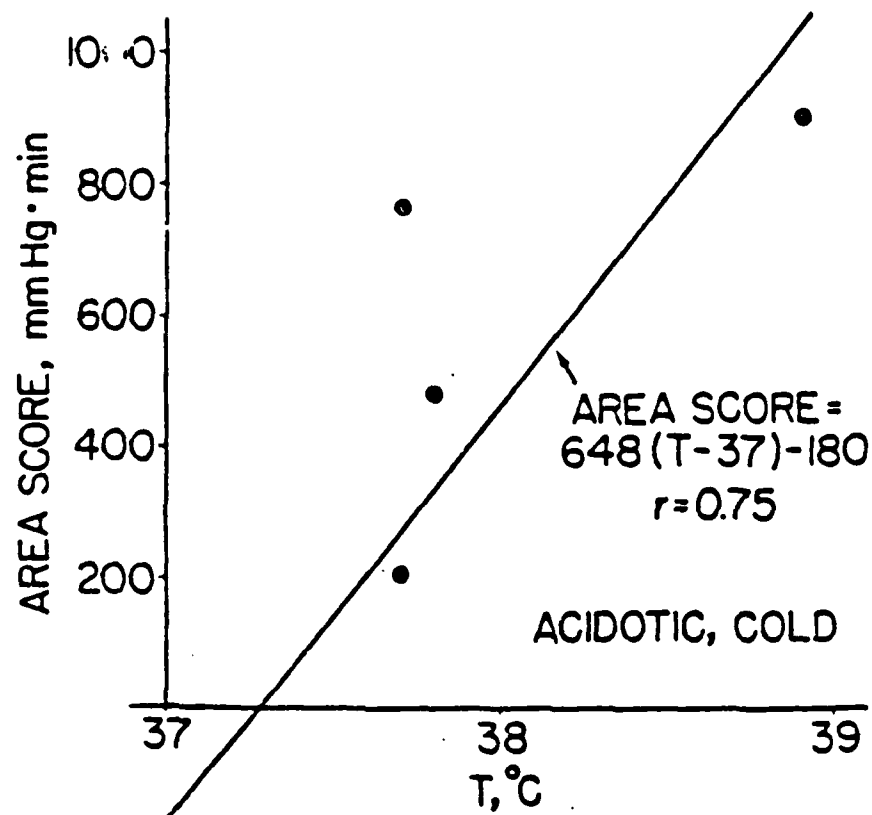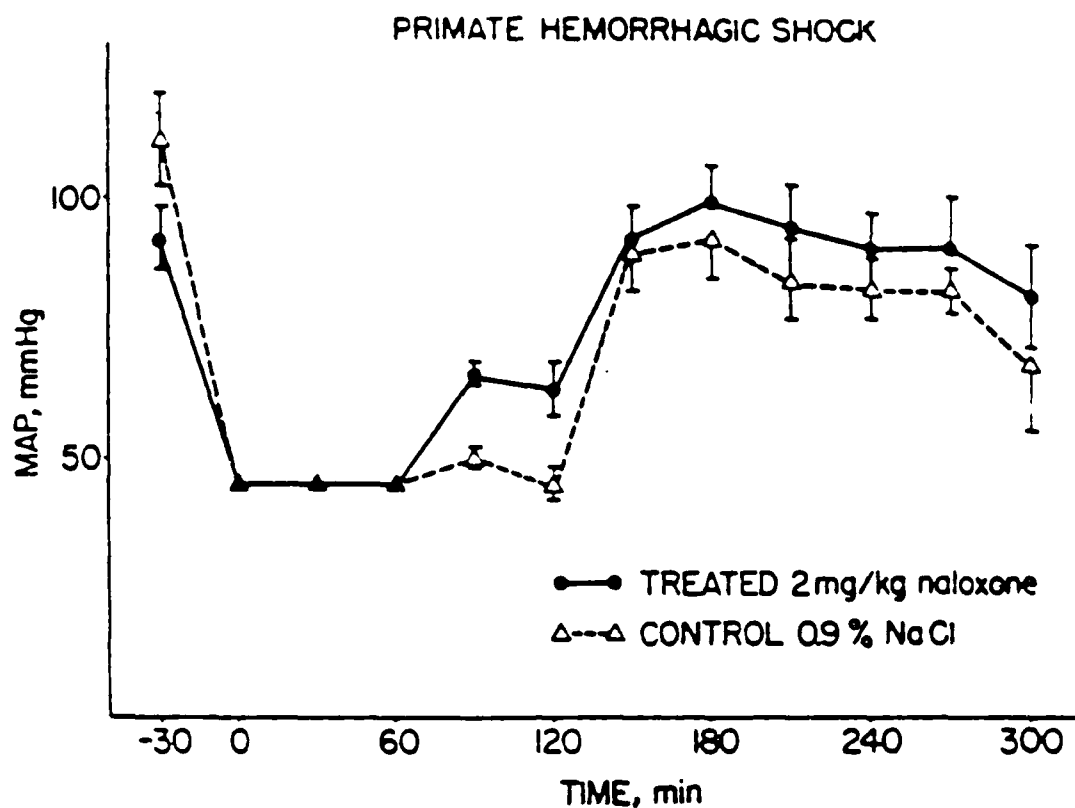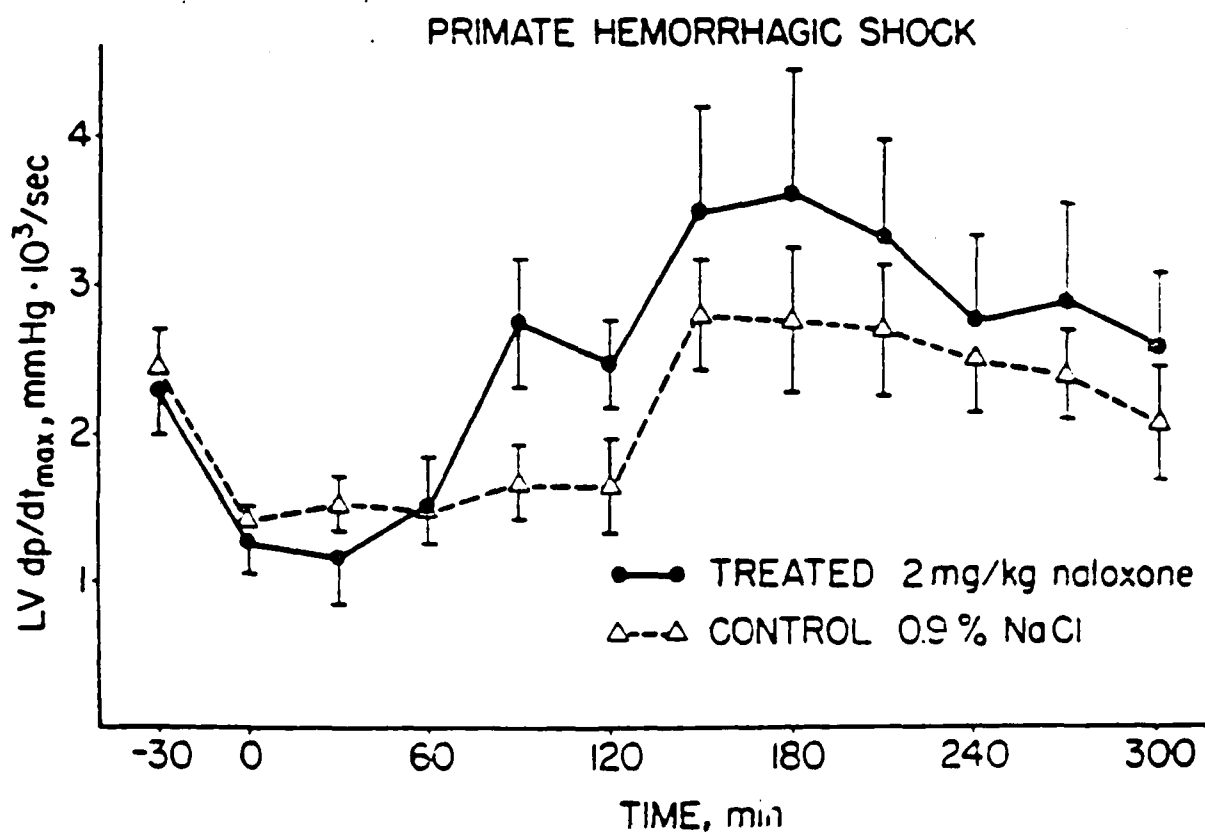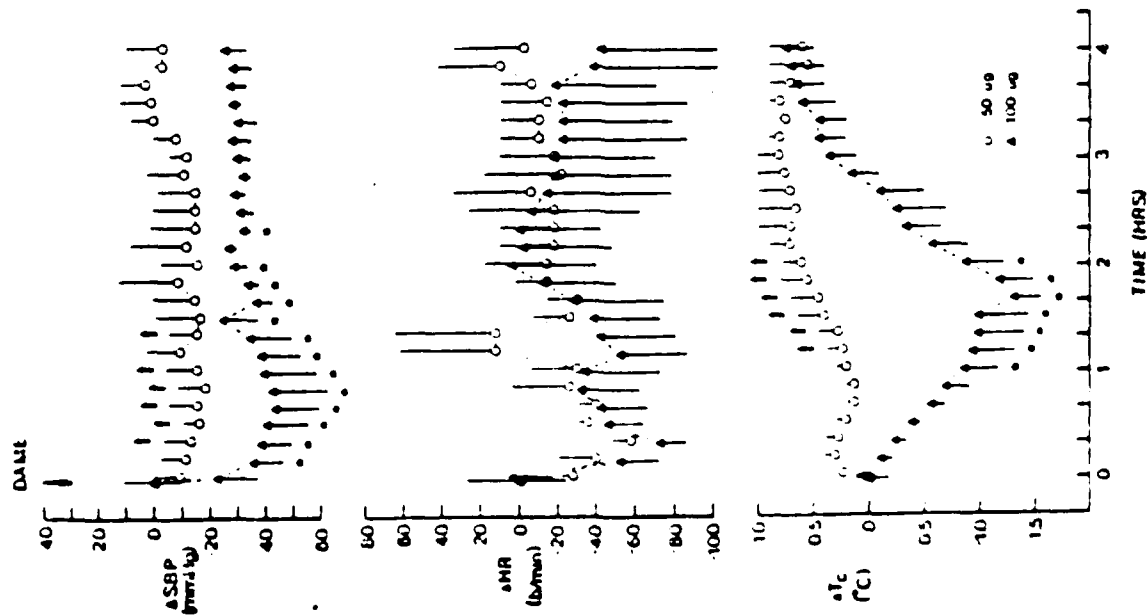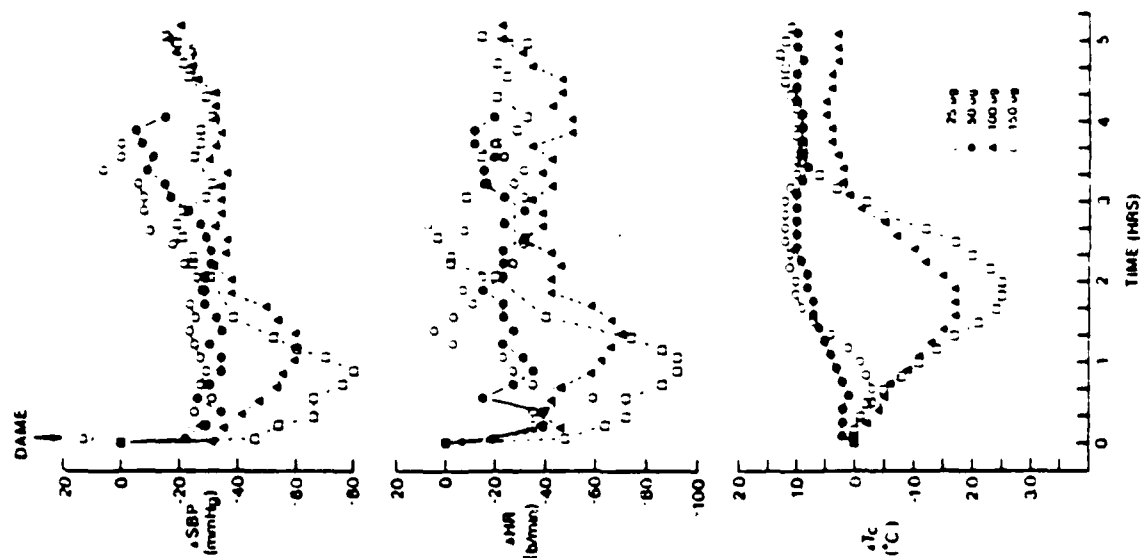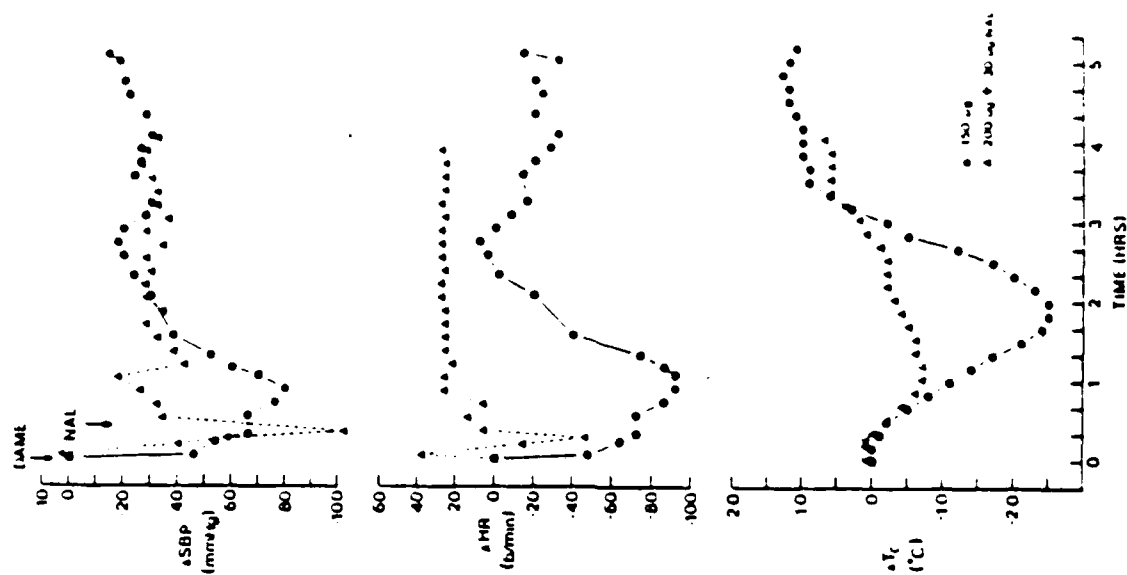
Figure 13b

Figure 13a
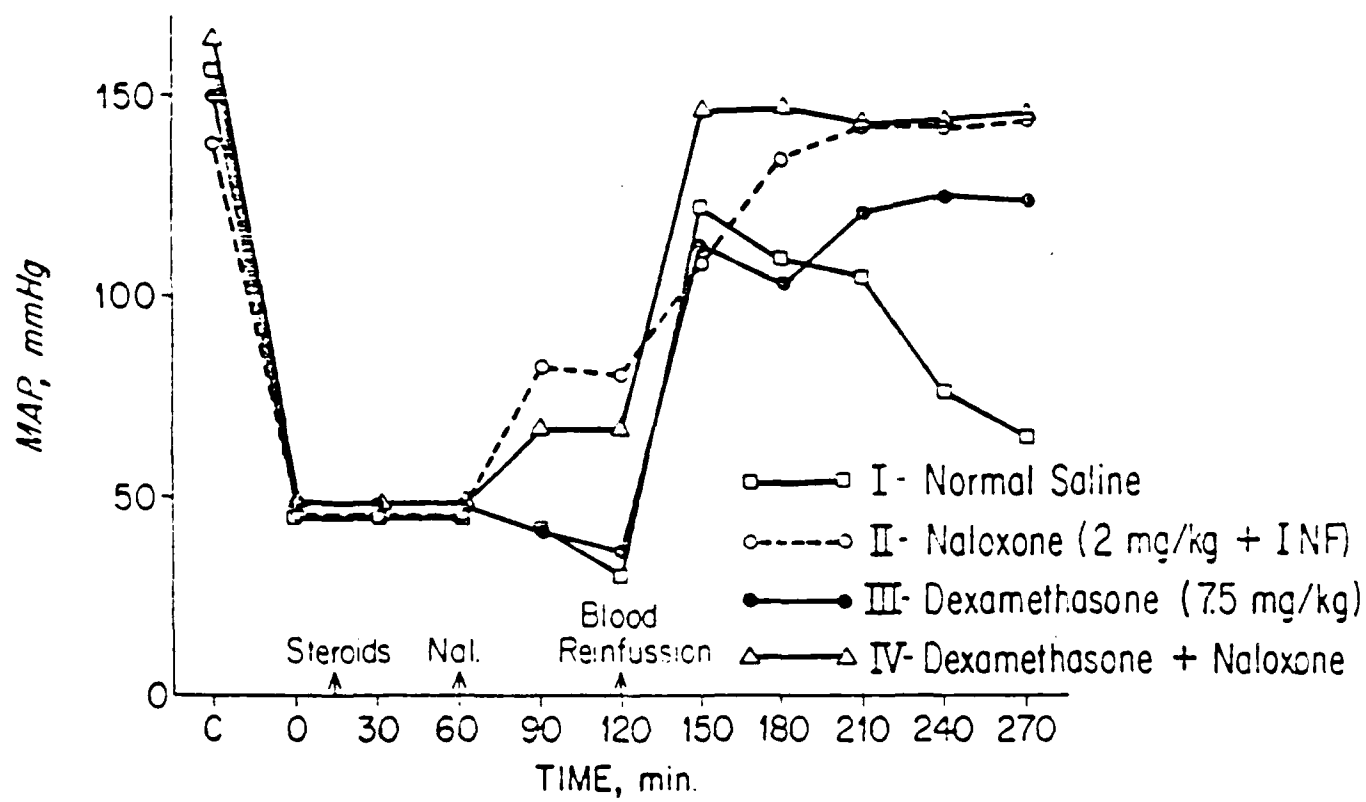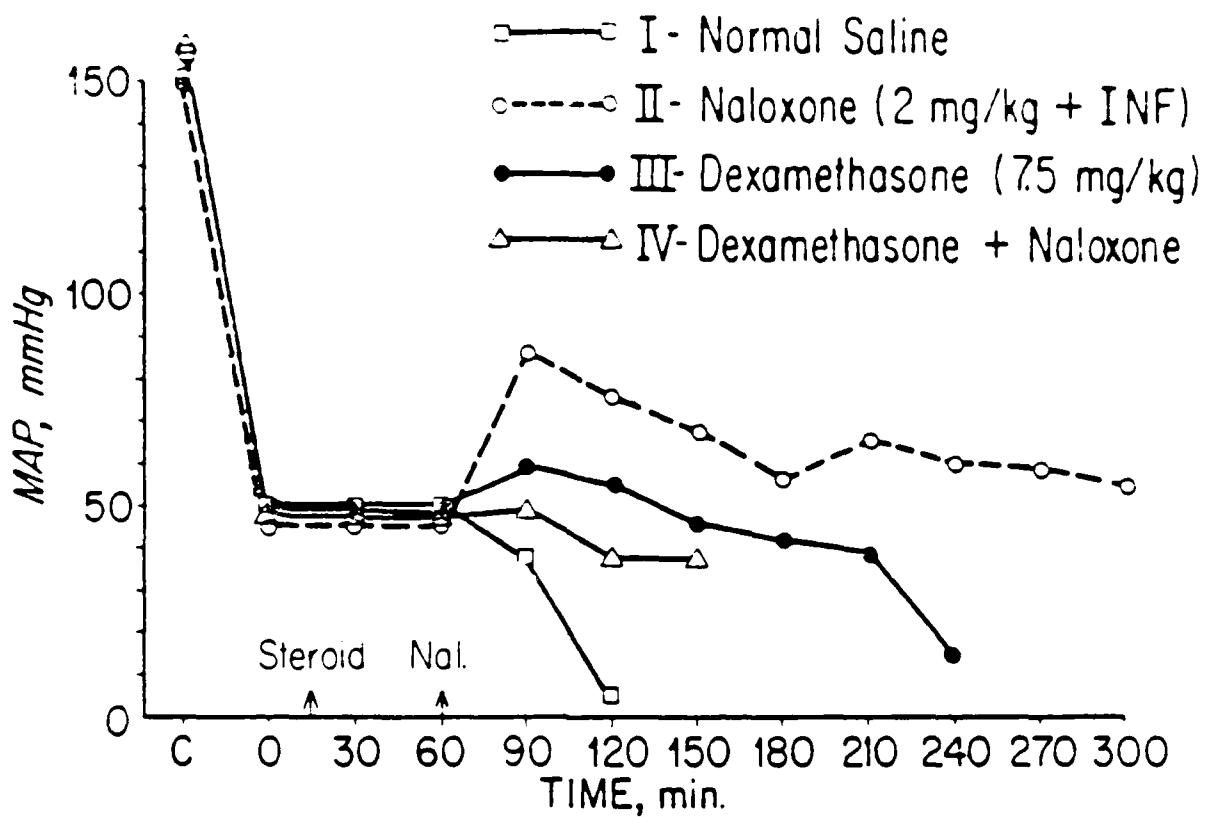
Figure 12

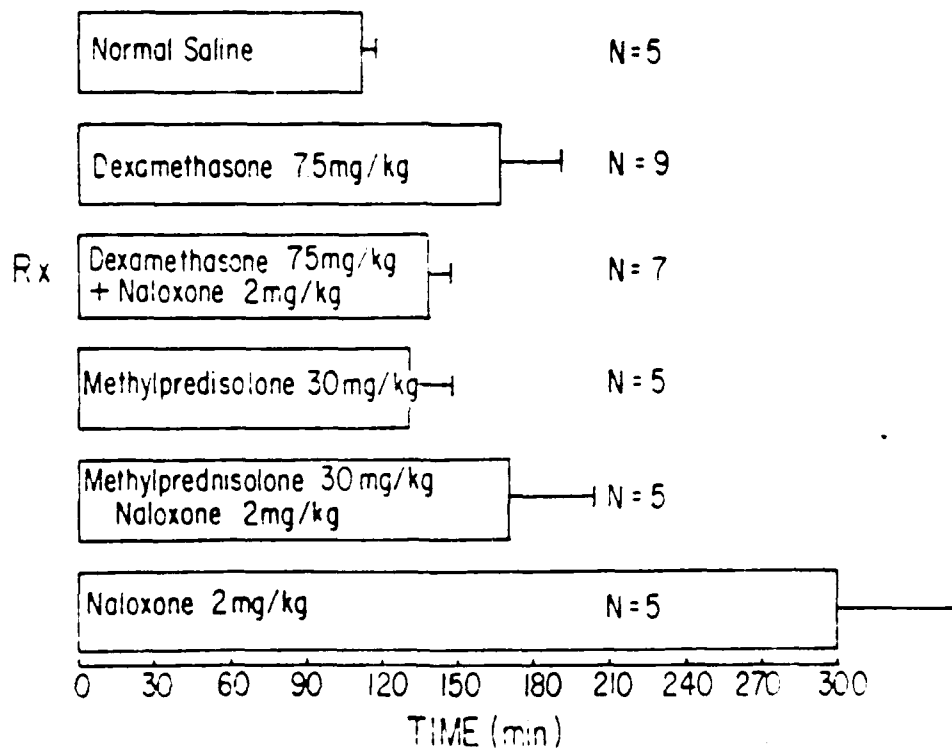Figure 1A

Figure 15

UNCOMPENSATED HEMORRHAGIC SHOCK, SURVIVAL
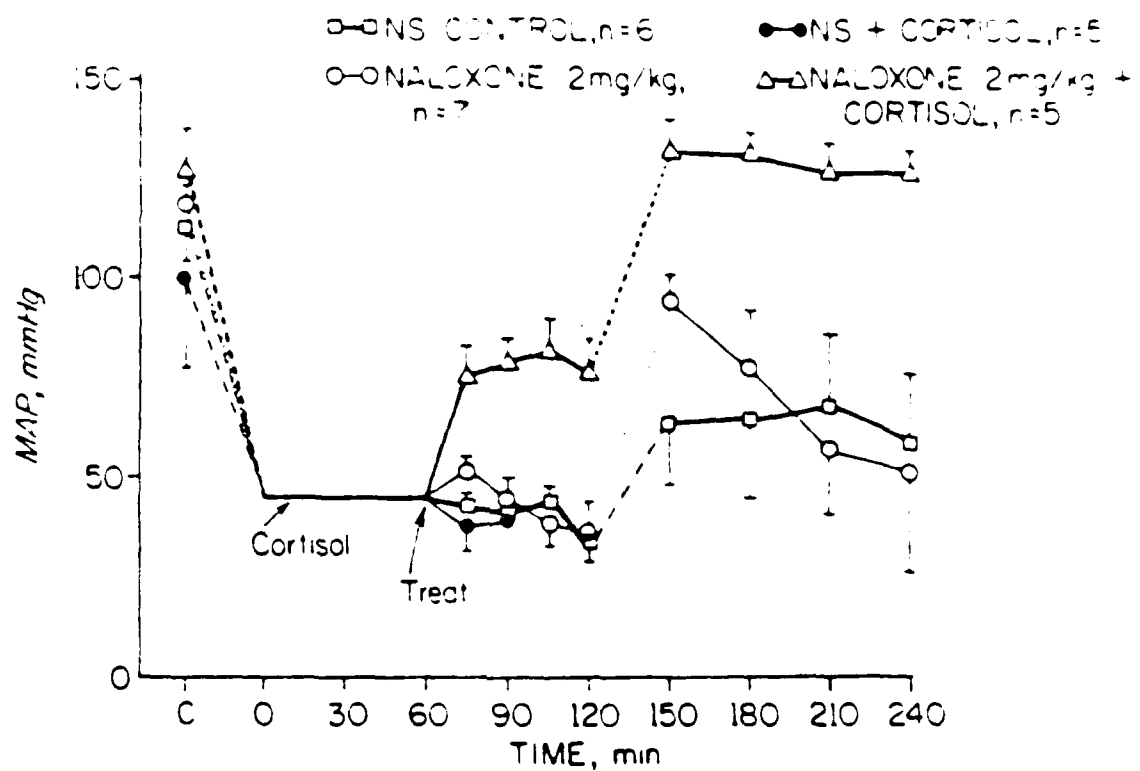

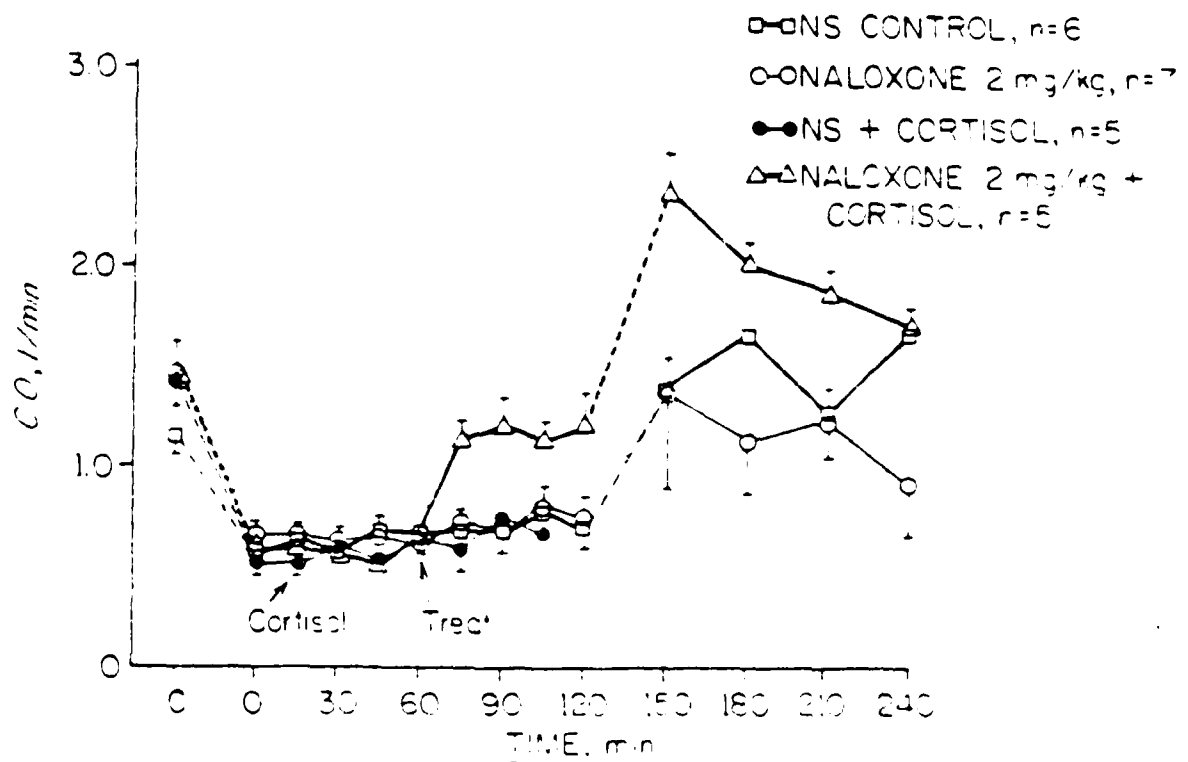Figure 16

CANINE HEMORRHAGIC SHOCK
Bilateral Adx / MAP

Figure 17
CANINE HEMORRHAGIC SHOCK
Bilateral Adx / C.O.

CANINE HEMORRHAGIC SHOCK
Bilateral Aox / dp/dt

□—NS CONTROL, n=6
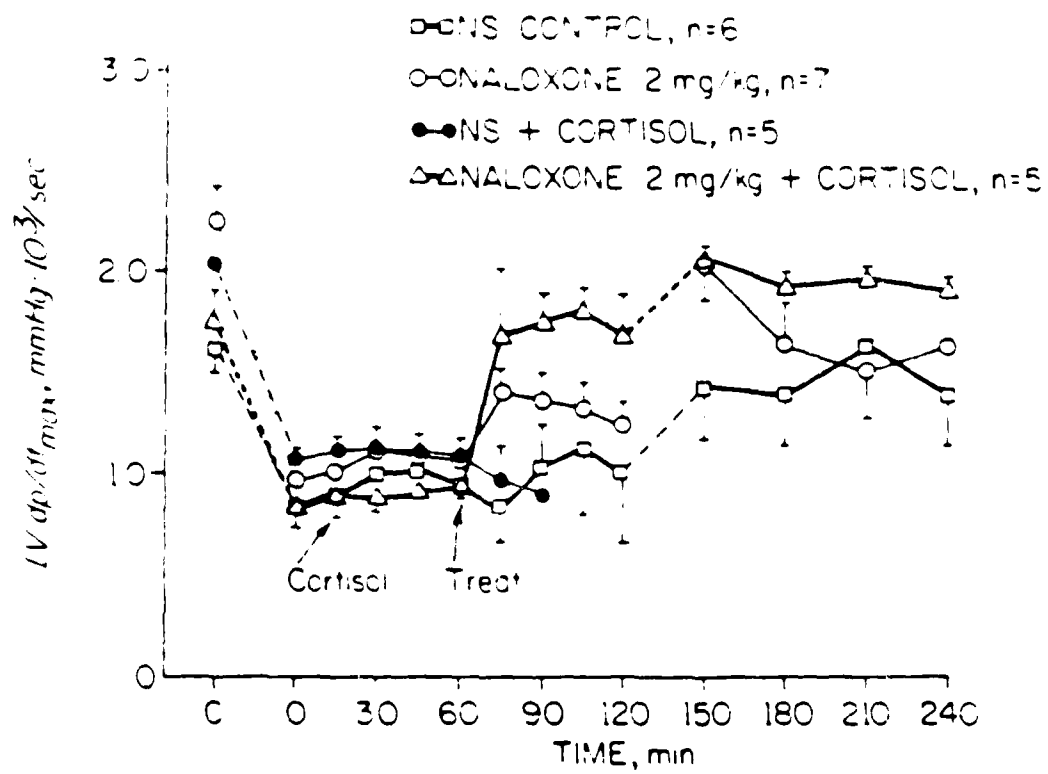○—NALOXONE 2 mg/kg, n=7
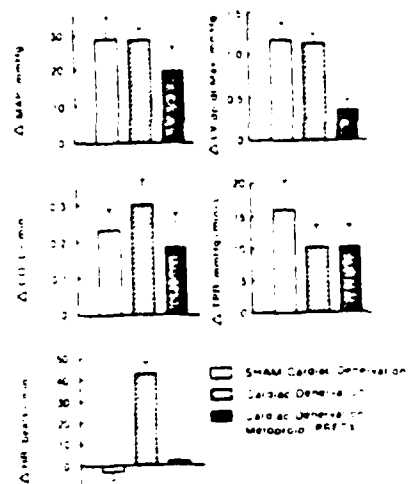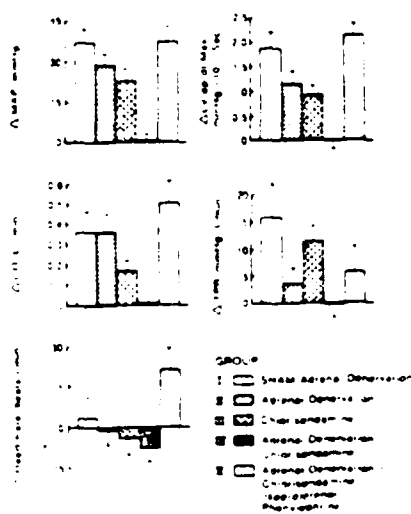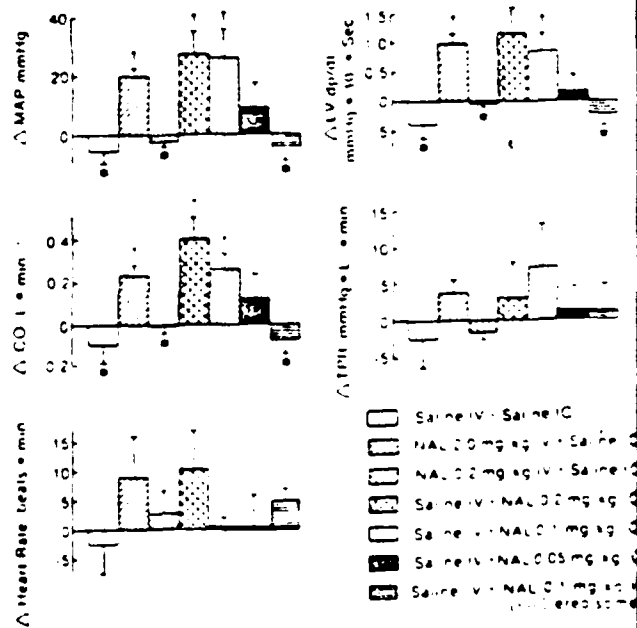●—NS + CORTISOL, n=5
△—NALOXONE 2 mg/kg + CORTISOL, n=5
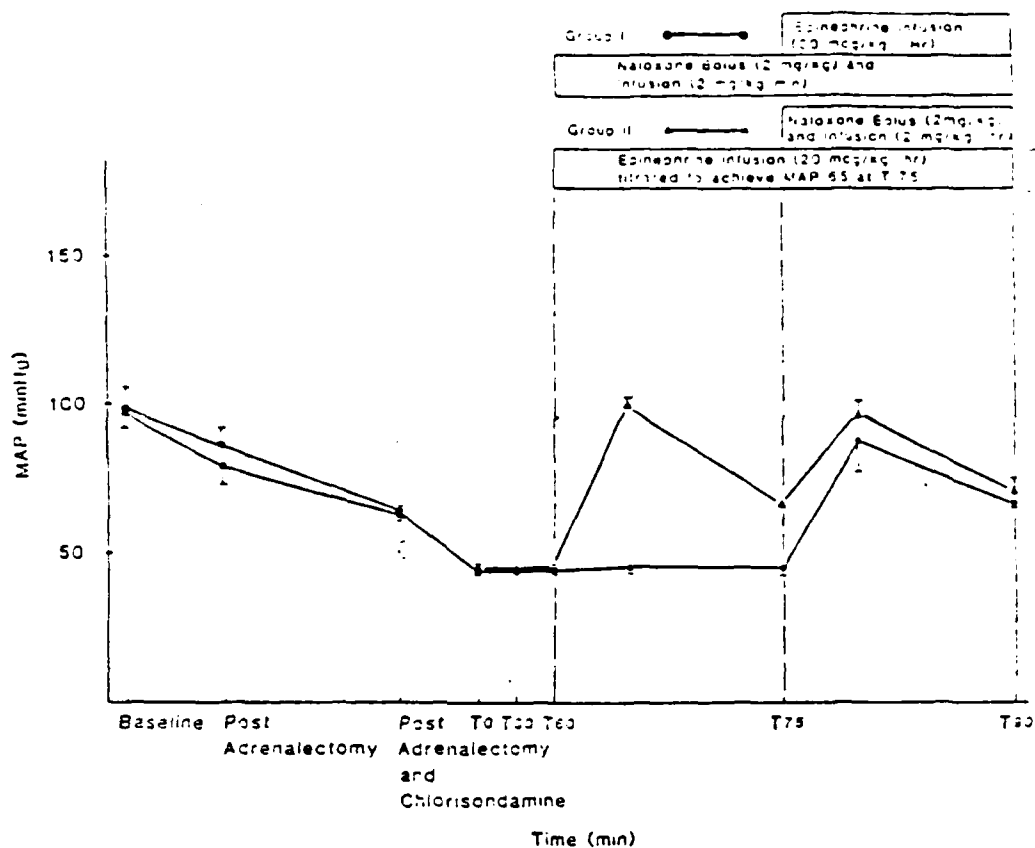
Figure 19

Figure 20

Figure 21

Figure 22

Figure 23

-39-

Figure 24
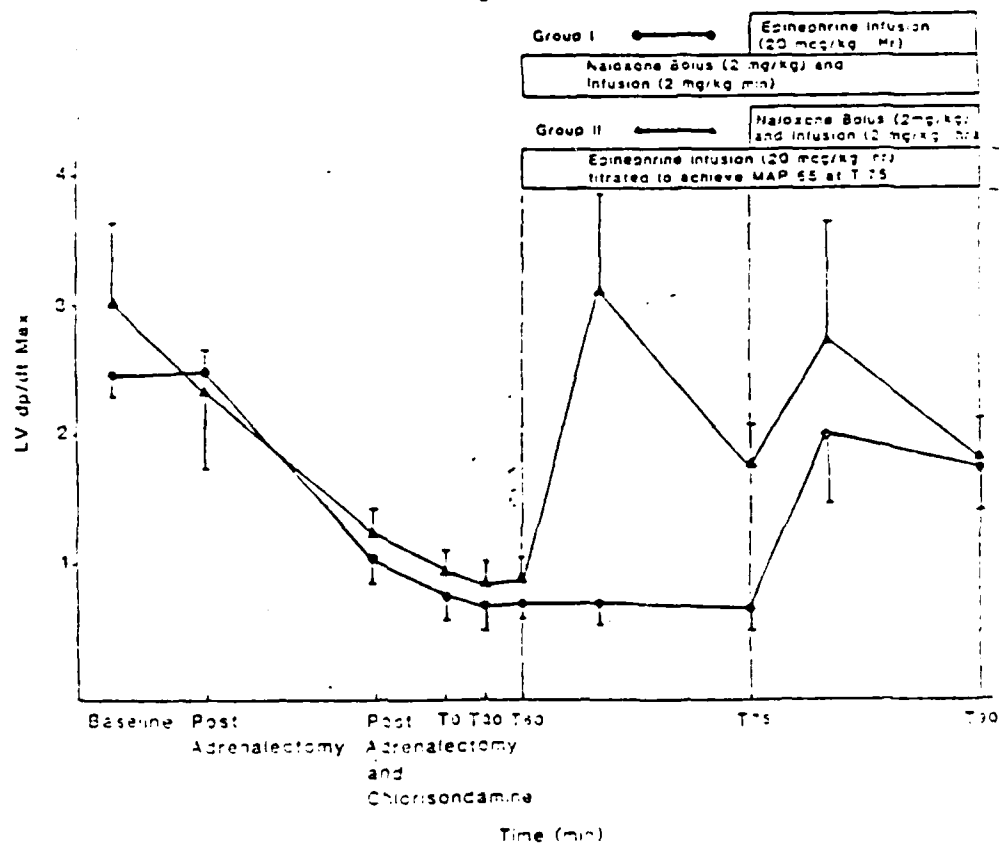

Figure 25
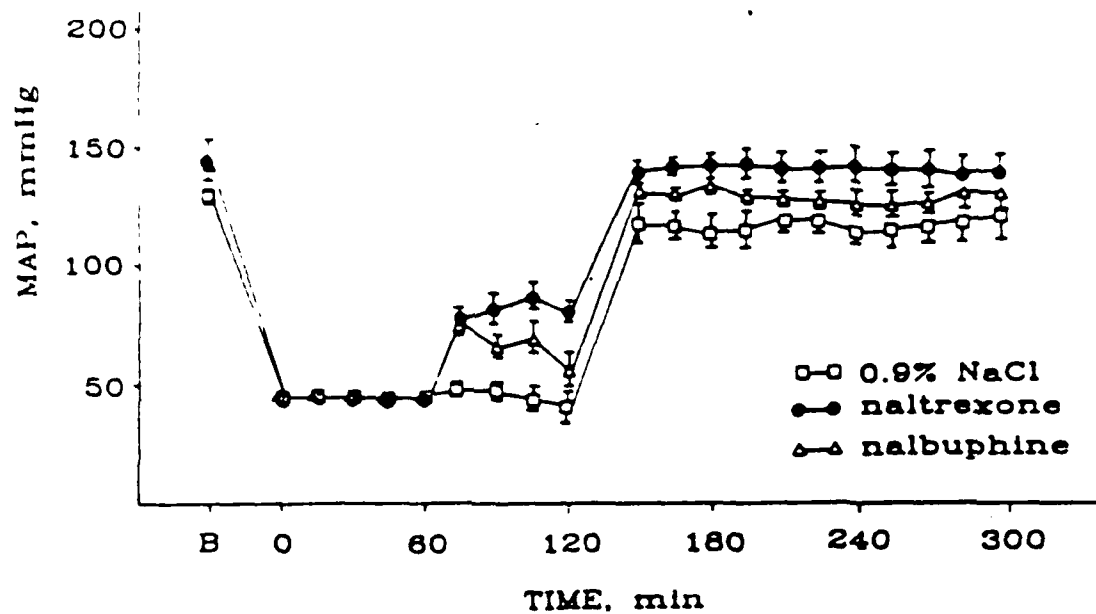
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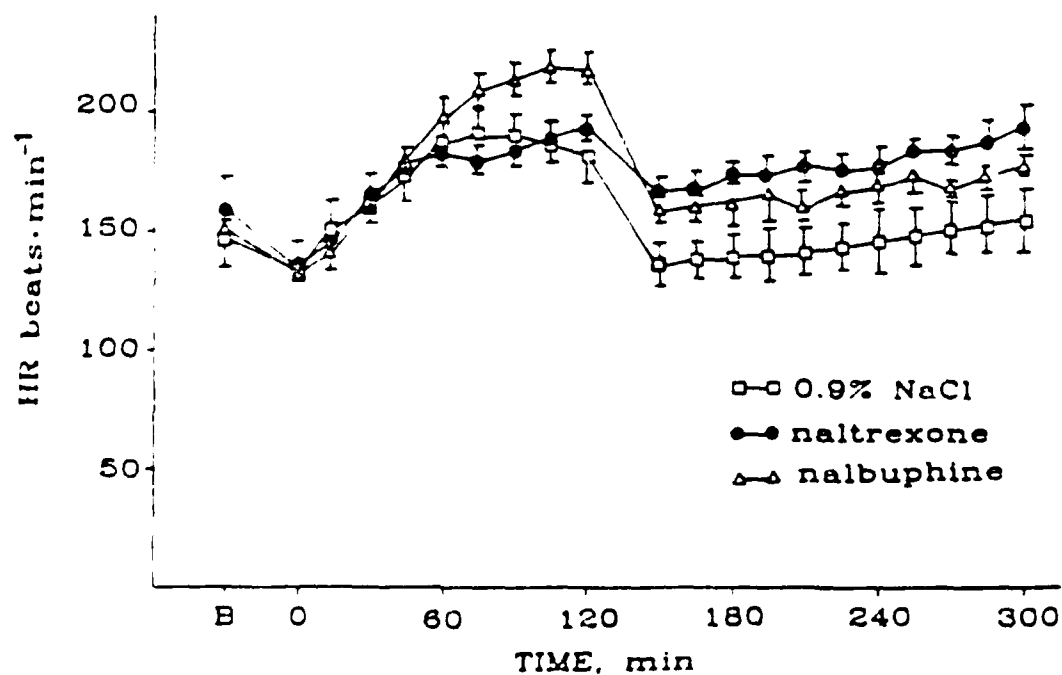
Figure 27
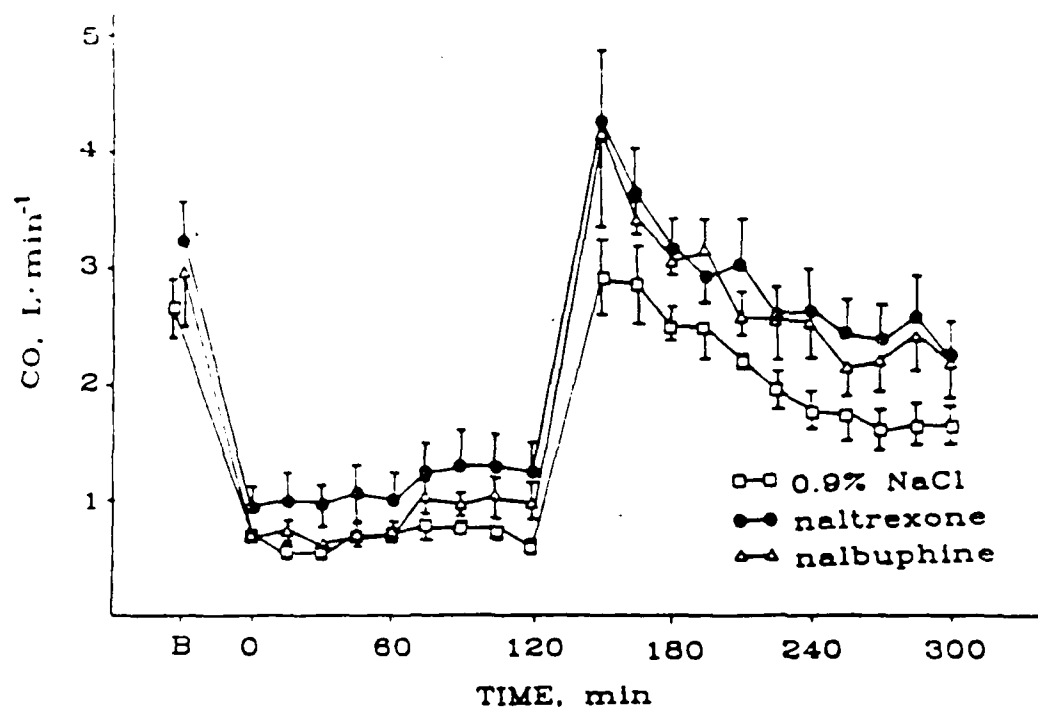
Figure 28
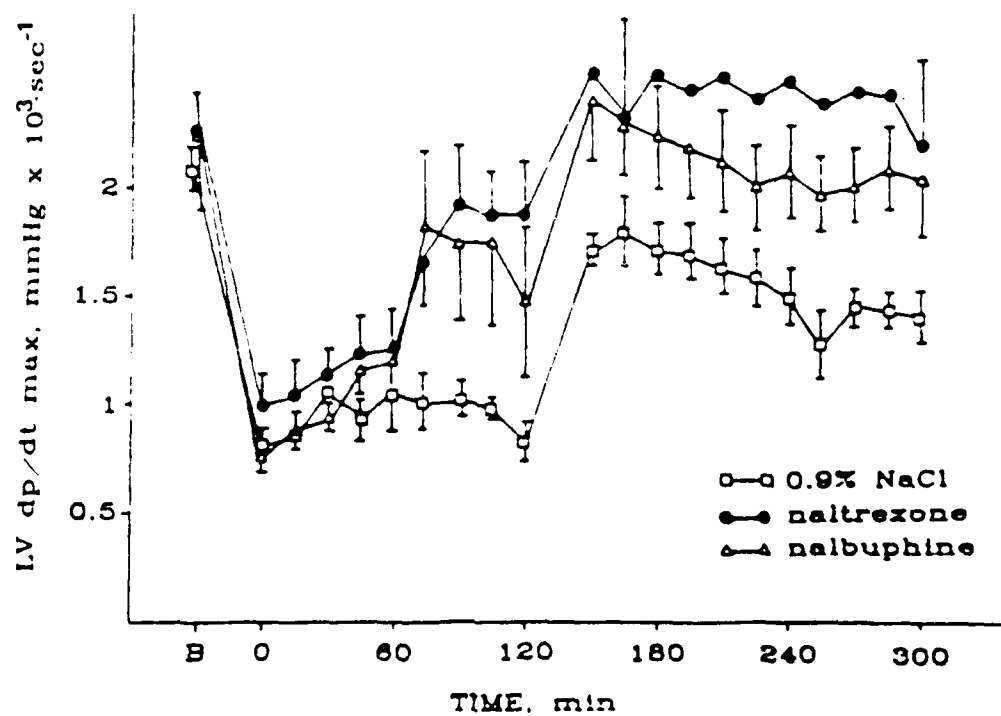
Figure 29

TRH IN PRIMATE HEMORRHAGIC SHOCK
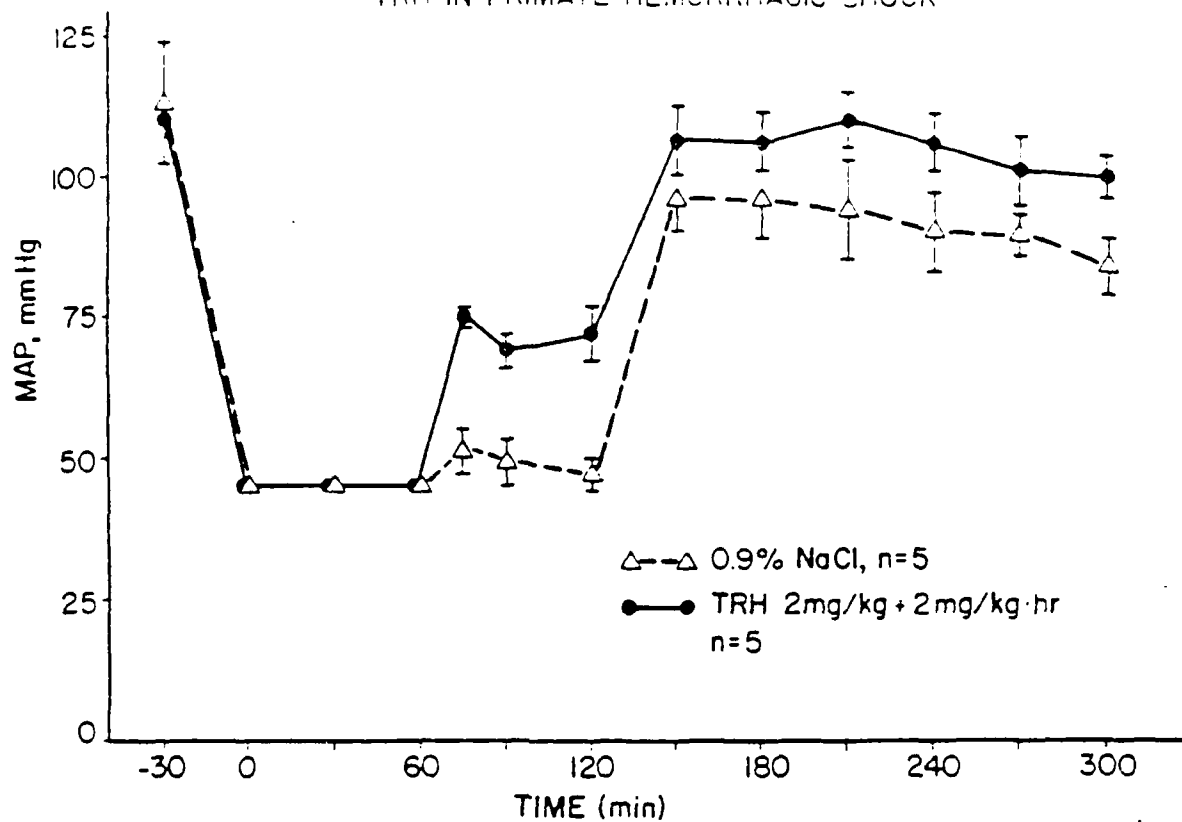
Figure 30.

TRH IN PRIMATE HEMORRHAGIC SHOCK
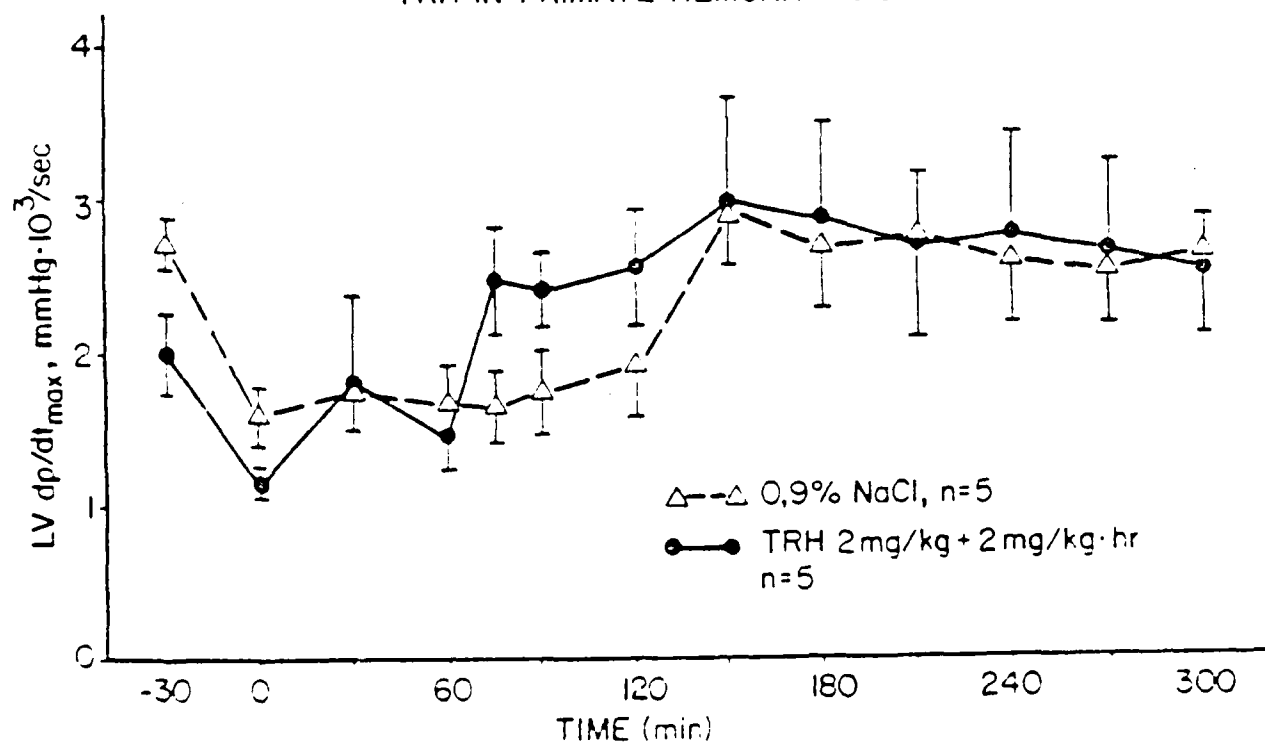
Figure 31

EFFECT OF TRH IN PRIMATE ENDOTOXIC SHOCK
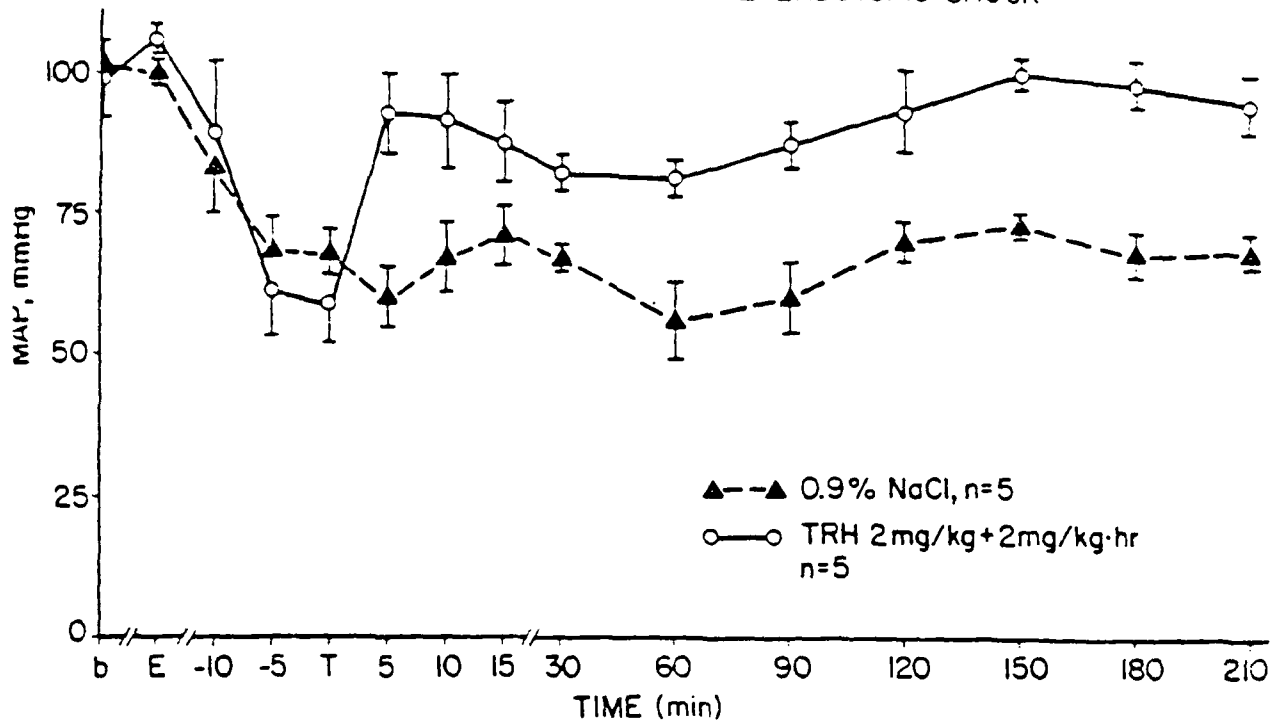
Figure 32

EFFECT OF TRH IN PRIMATE ENDOTOXIC SHOCK
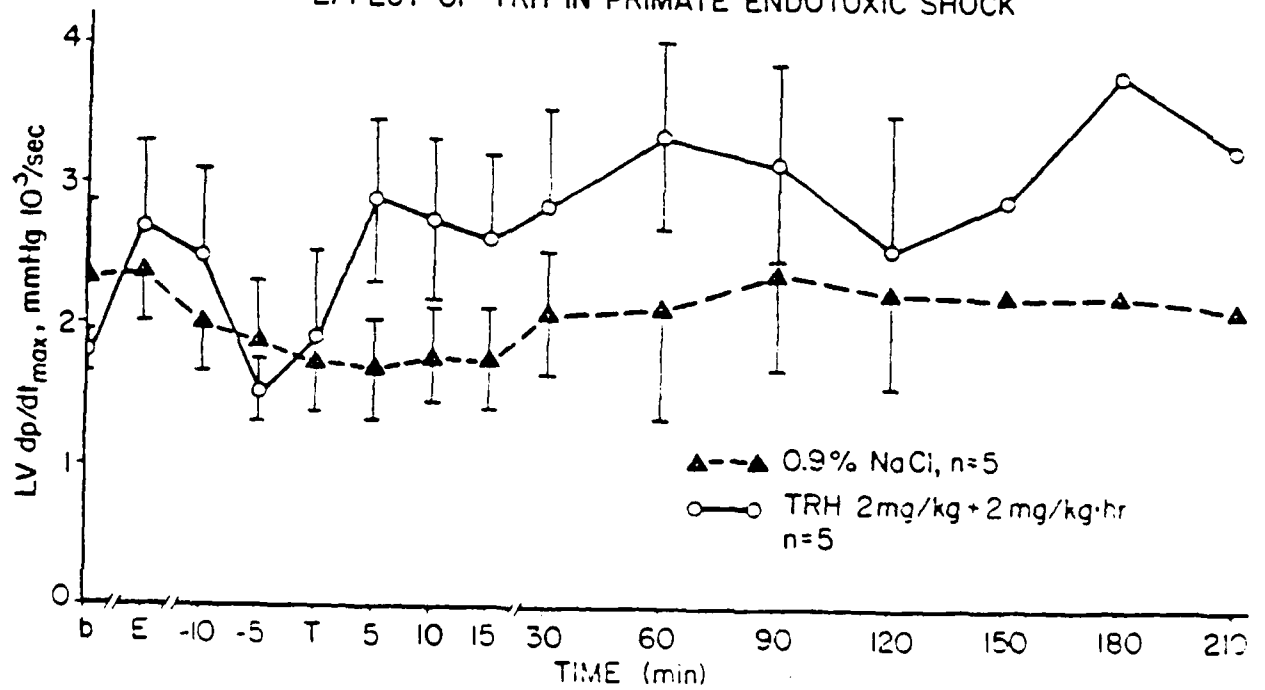
Figure 33
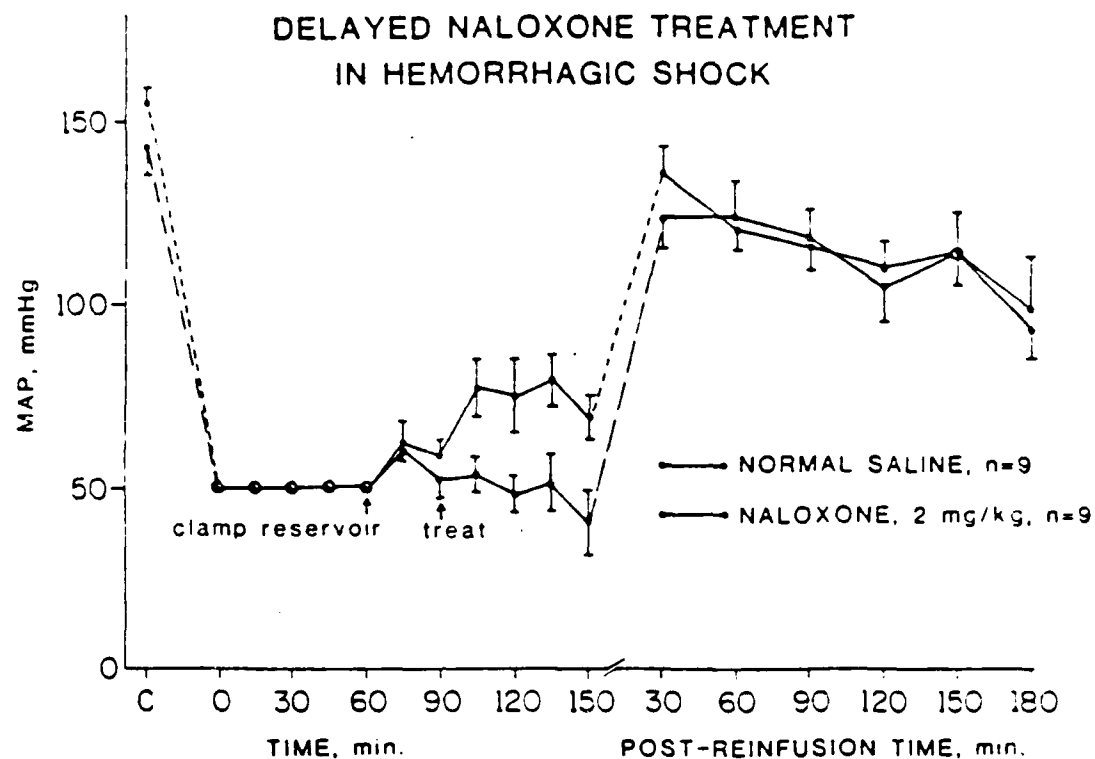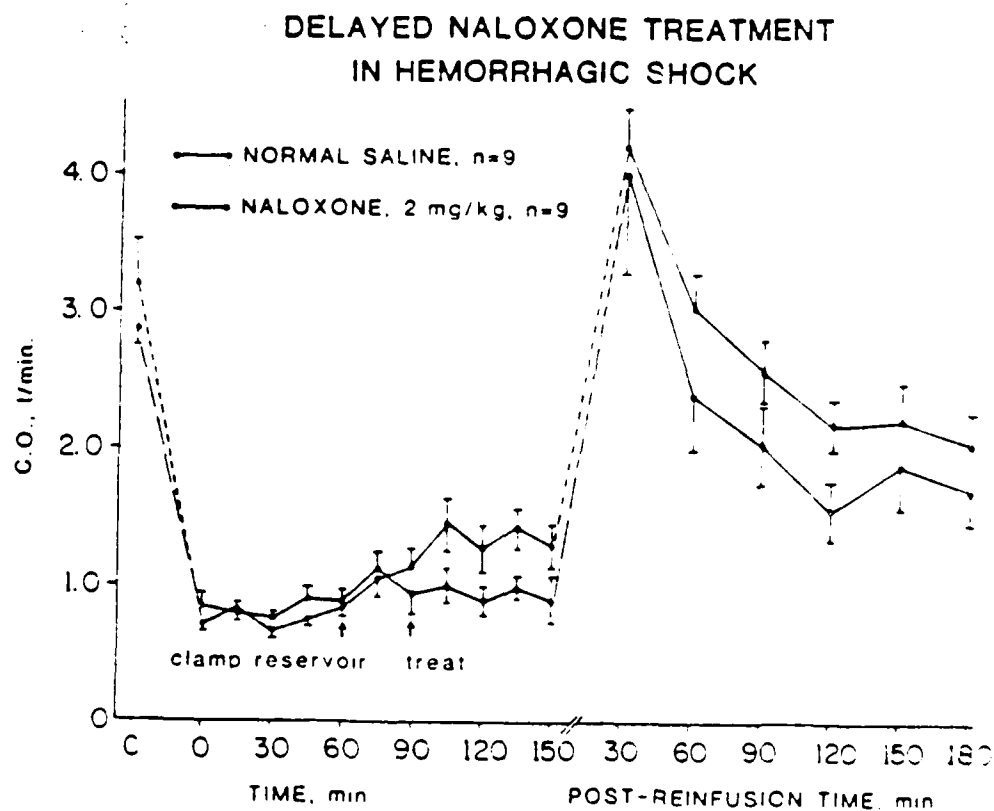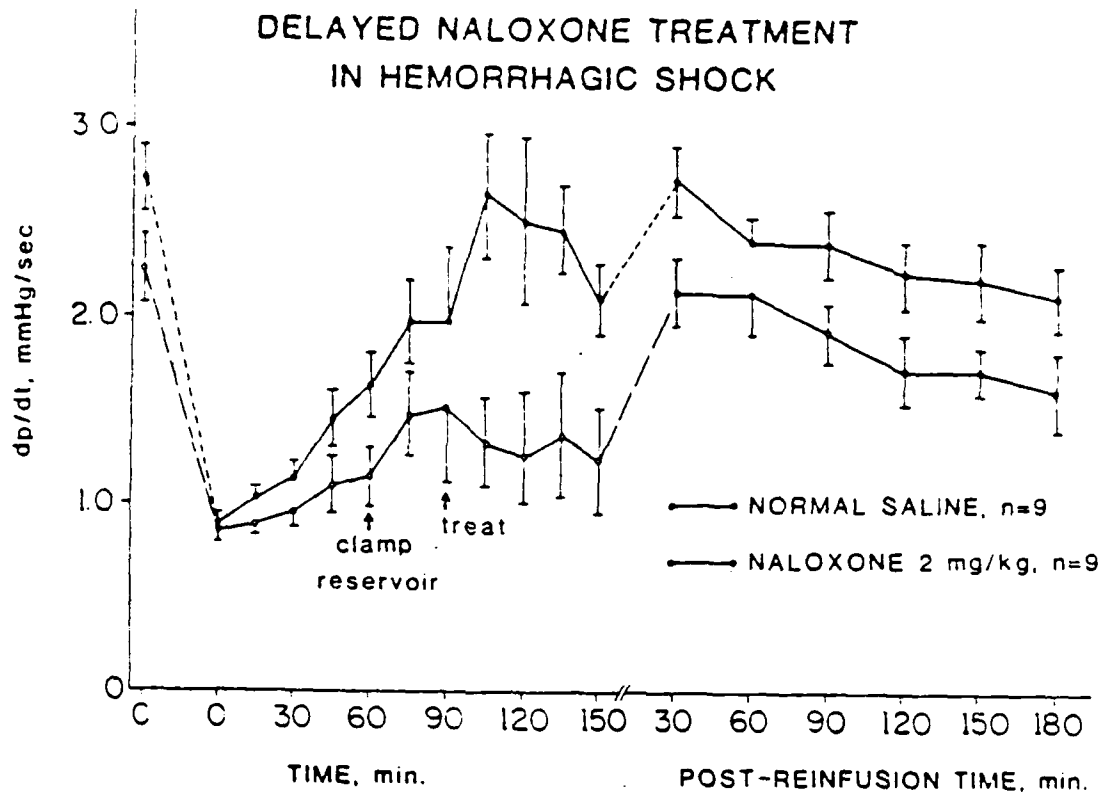
DELAYED NALOXONE TREATMENT
IN HEMORRHAGIC SHOCK

Figure 34

DELAYED NALOXONE TREATMENT
IN HEMORRHAGIC SHOCK

Figure 35

DELAYED NALOXONE TREATMENT
IN HEMORRHAGIC SHOCK

Figure 36

DELAYED NALOXONE TREATMENT
IN HEMORRHAGIC SHOCK

Figure 37

-42-
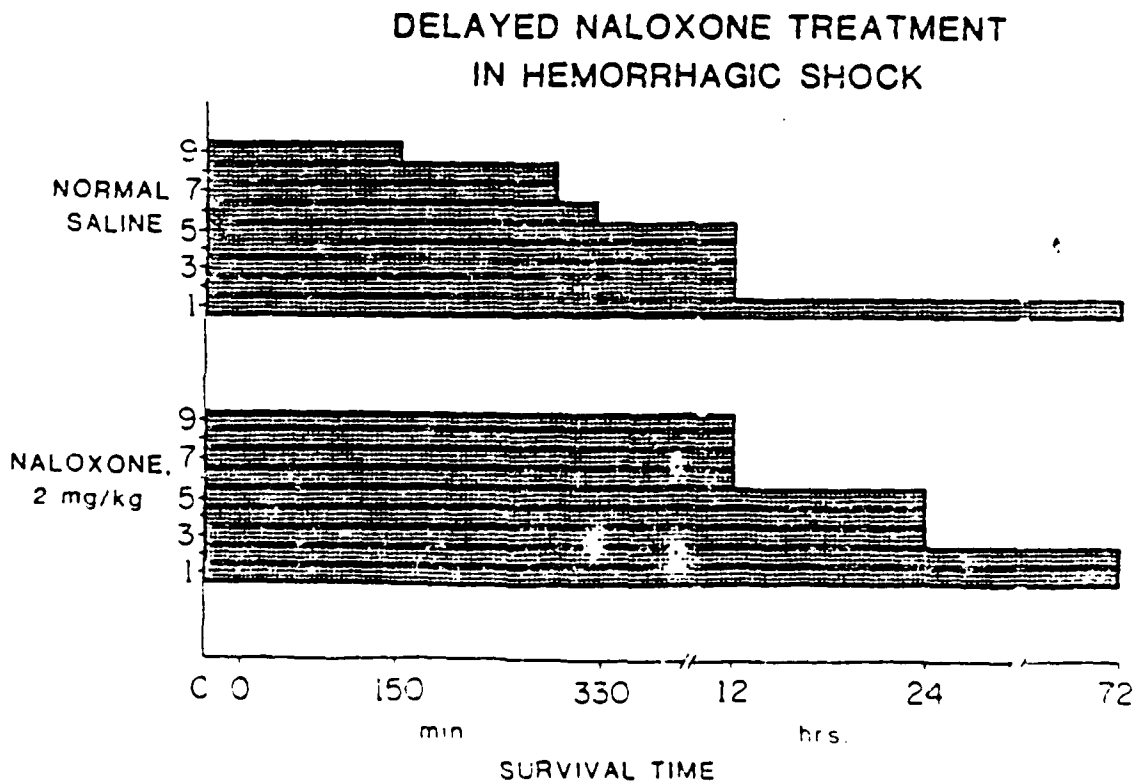
INTRACEREEROVENTRICULAR NALOXONE IN CANINE HYPOVOLEMIC SHOCK
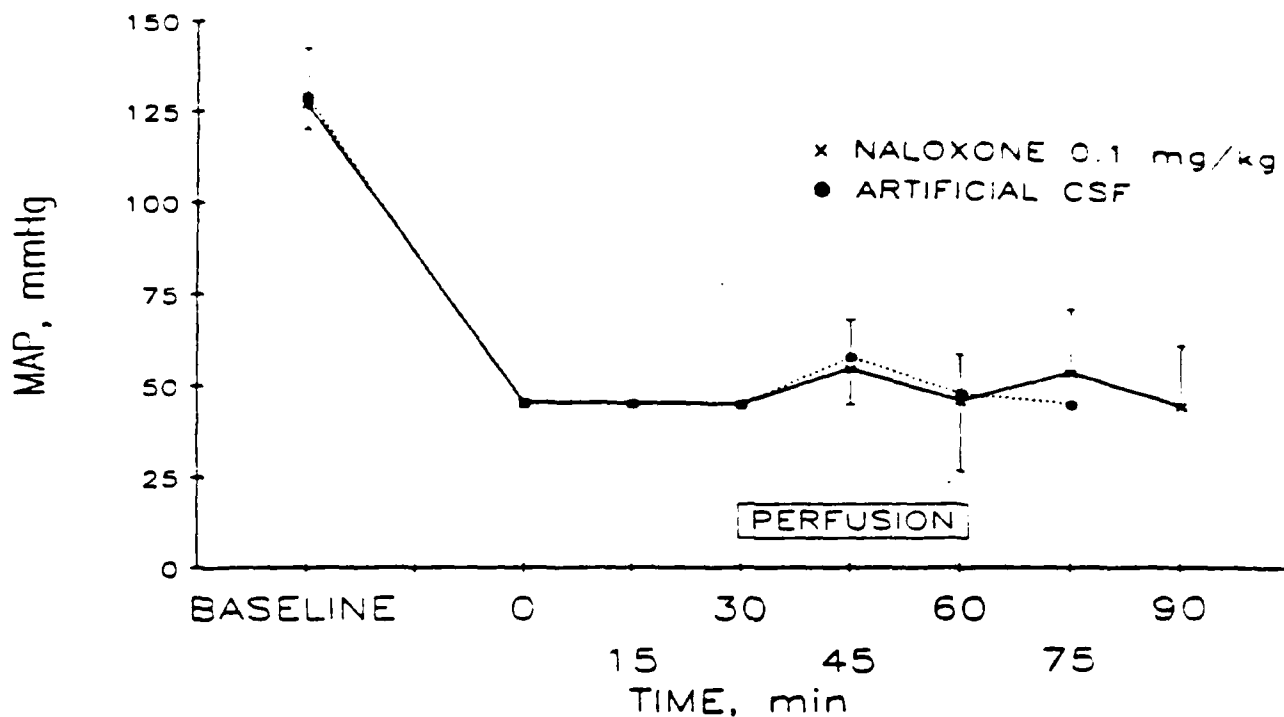
Figure 38

INTRACEREBROVENTRICULAR NALOXONE IN CANINE HYPOVOLEMIC SHOCK
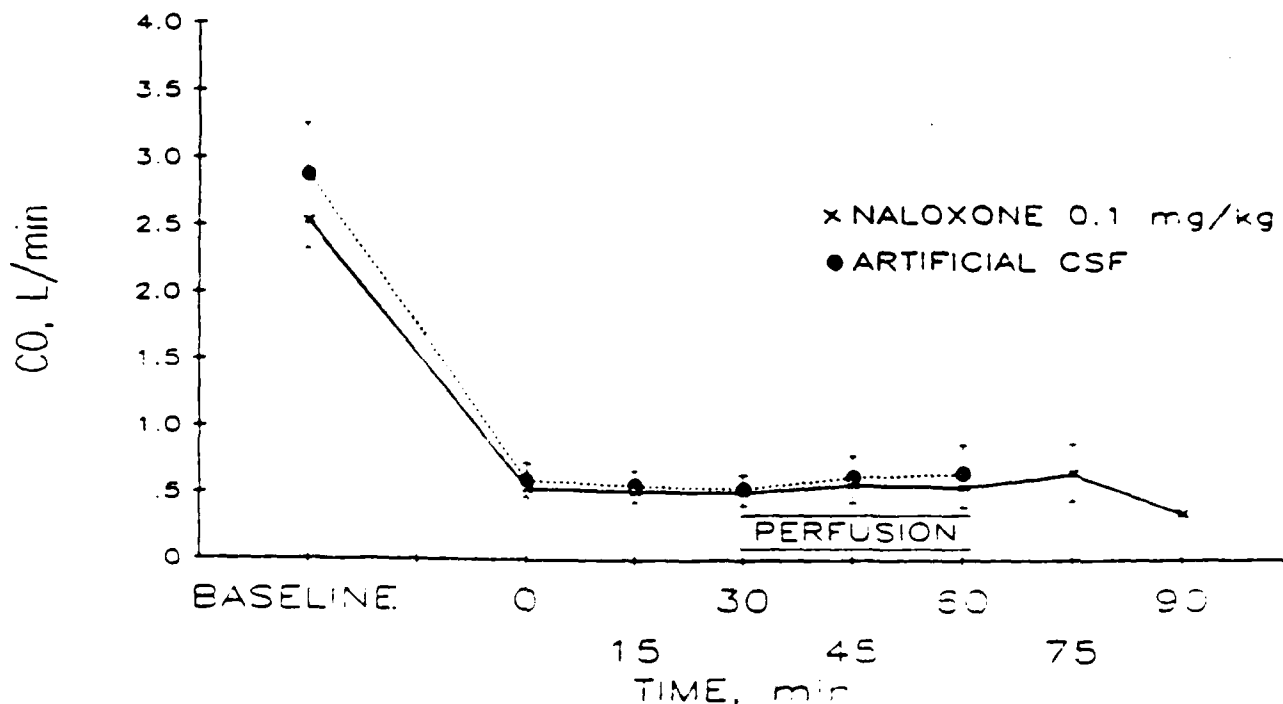
Figure 39

INTRACEREBROVENTRICULAR NALOXONE IN CANINE HYPOVOLEMIC SHOCK
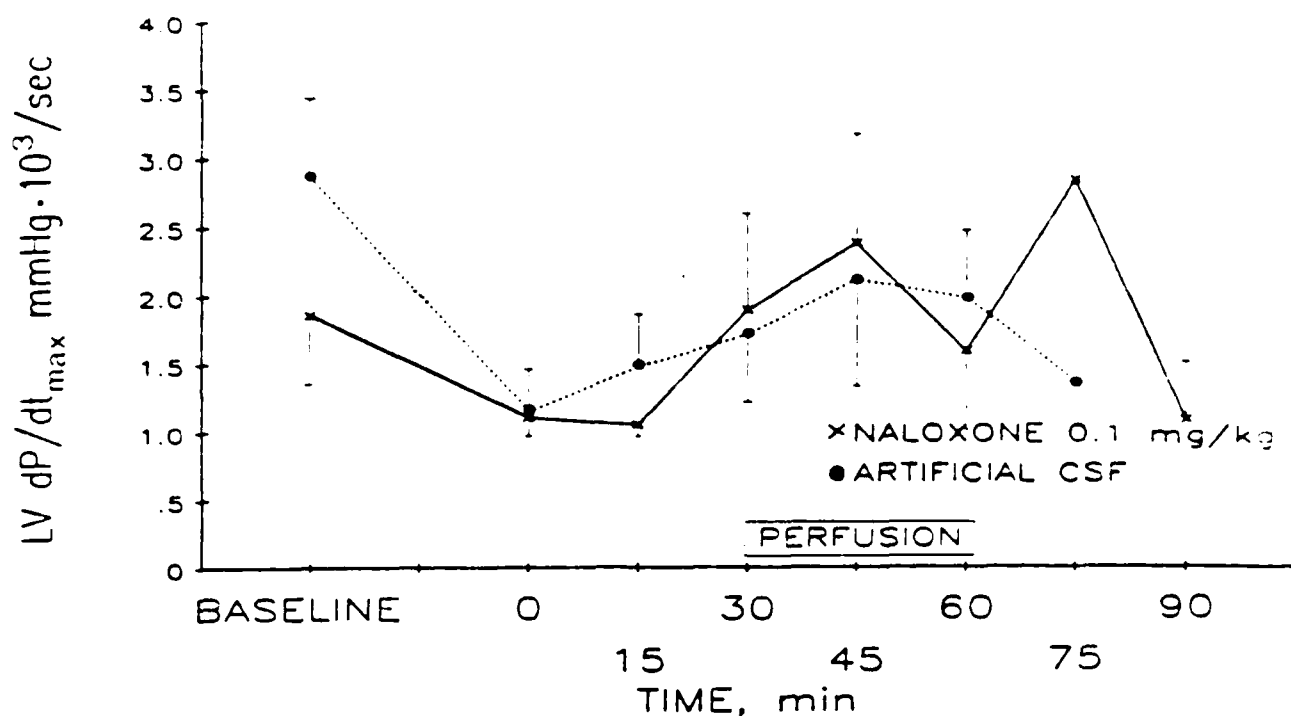
Figure 40

INTRACEREBROVENTRICULAR NALOXONE IN CANINE ENDOTOXEMIC SHOCK
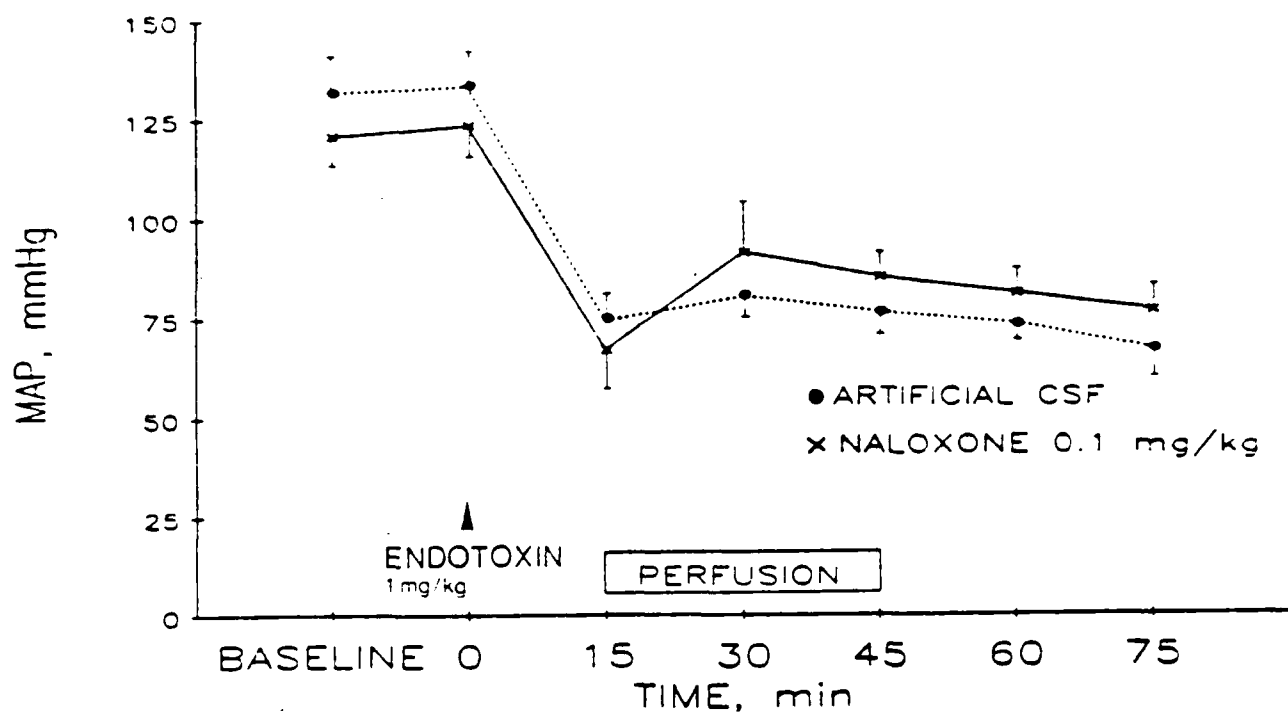
Figure 41

INTRACEREBROVENTRICULAR NALOXONE IN CANINE ENDOTOXEMIC SHOCK
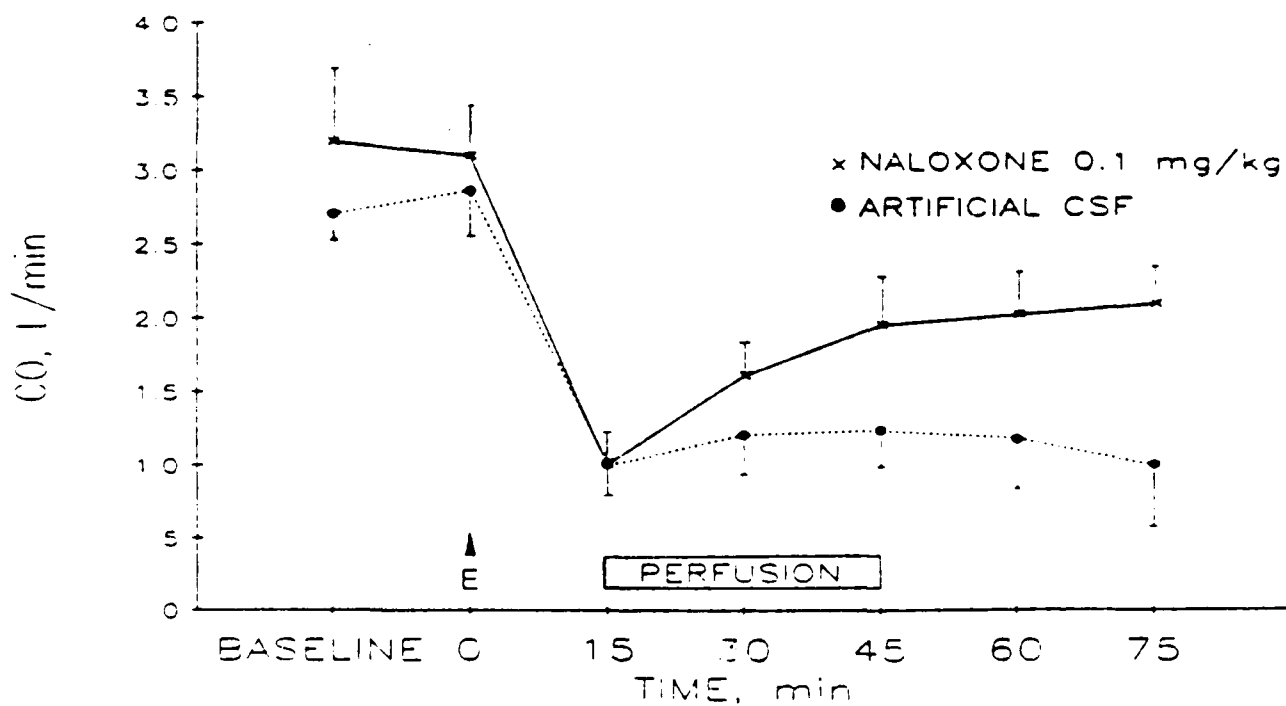
Figure 42

INTRACEREBROVENTRICULAR NALOXONE IN
CANINE ENDOTOXEMIC SHOCK
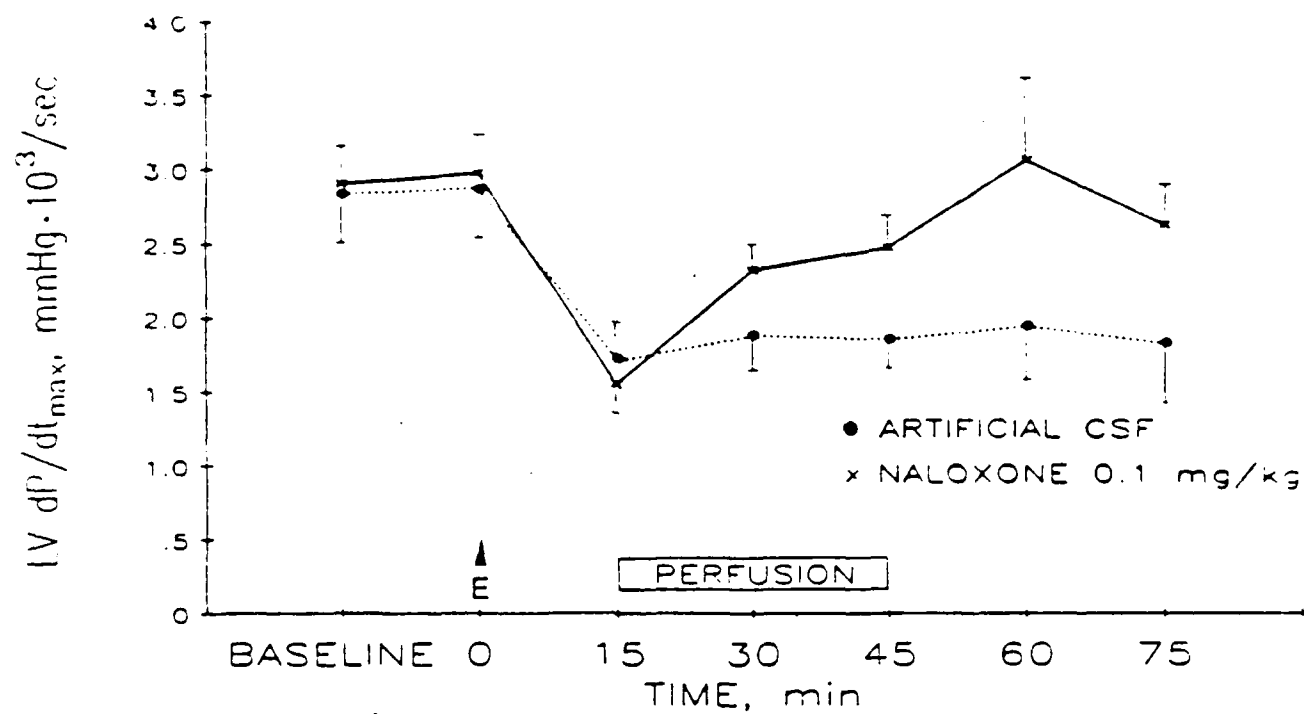
Figure 43

INTRATHECAL NALOXONE IN
CANINE HYPOVOLEMIC SHOCK
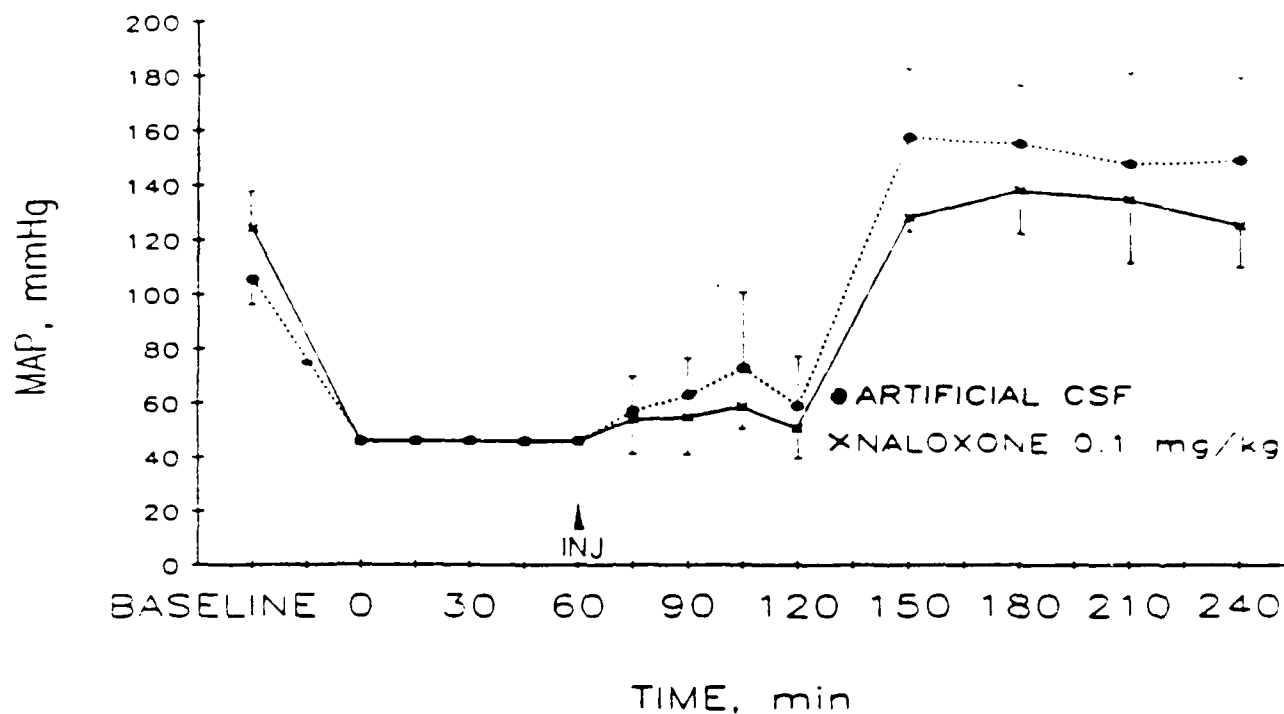
Figure 44

INTRATHECAL NALOXONE IN
CANINE HYPOVOLEMIC SHOCK
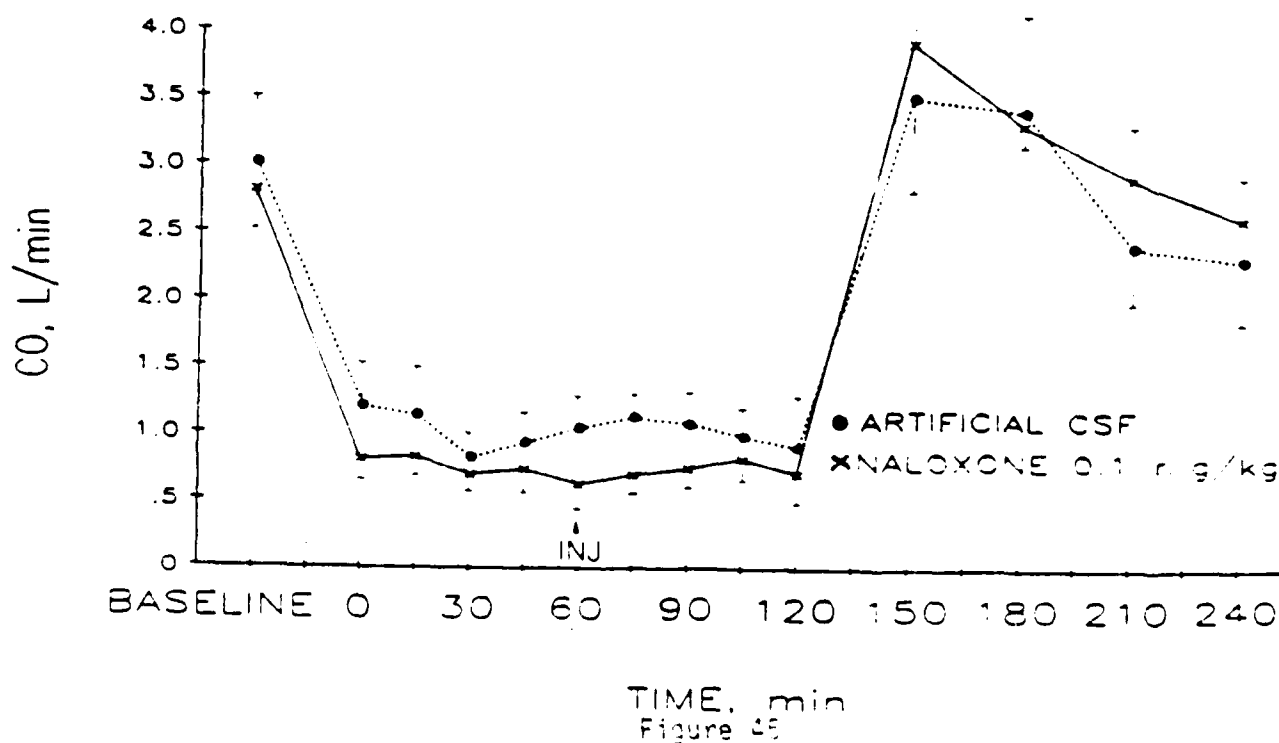
Figure 45

INTRATHECAL NALOXONE IN CANINE HYPOVOLEMIC SHOCK
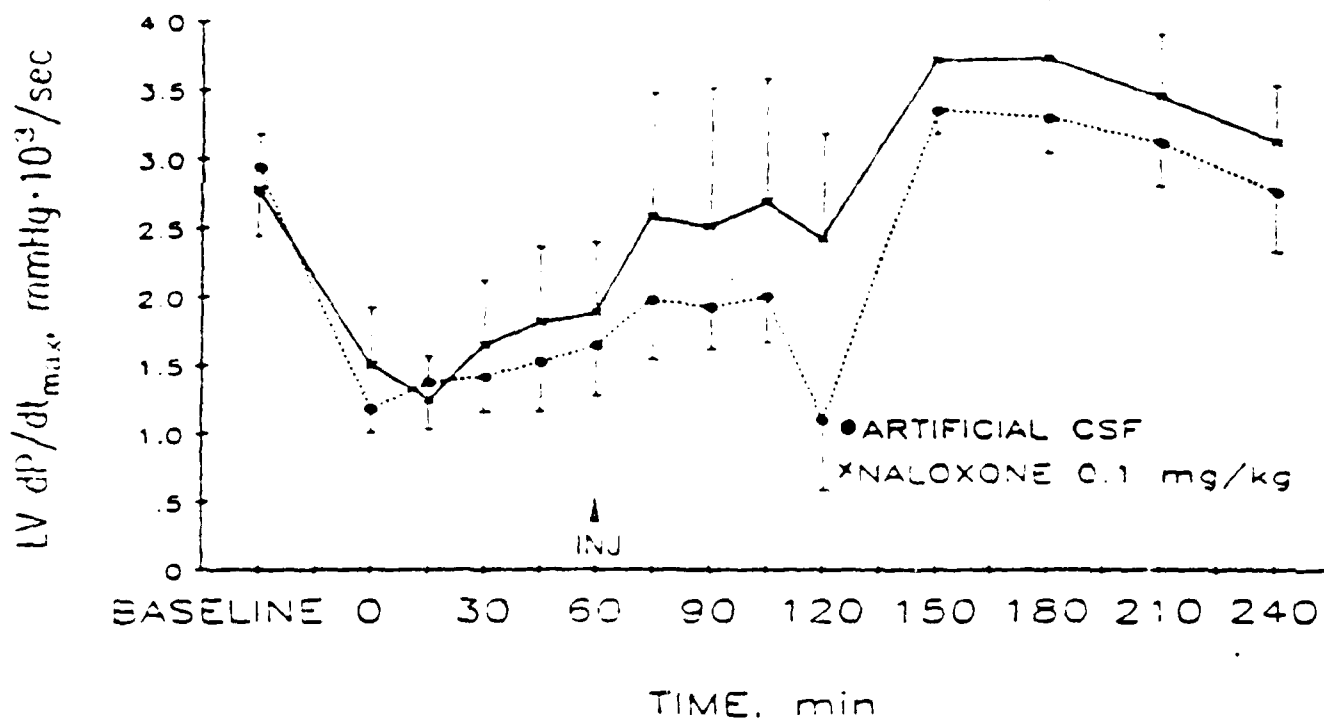
TIME, min

Figure 4B
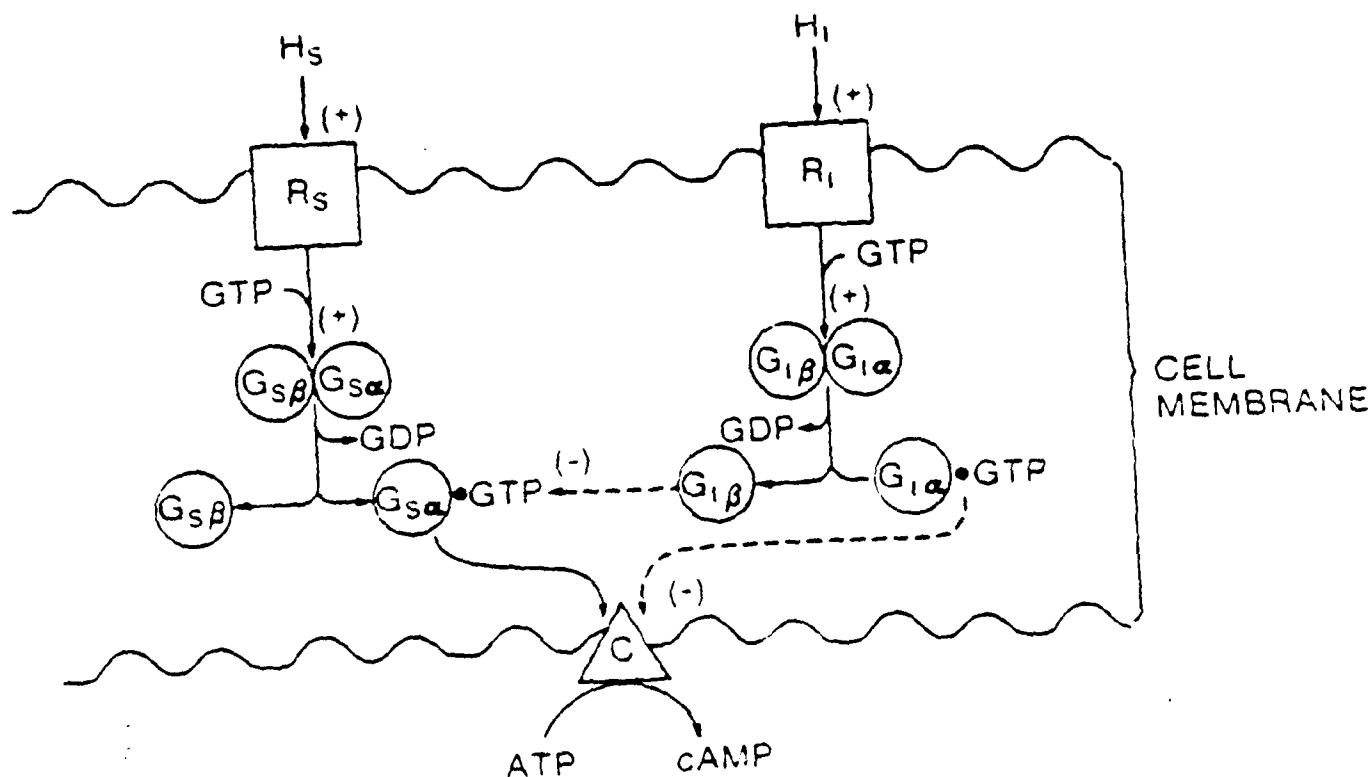
Hs = STIMULATORY HORMONE
  β-adrenergic agonists
  Dopamine
  Prostaglandins
  Peptide Hormones

Hi = INHIBITORY HORMONE
  Opioids

GTP = GUANOSINE TRIPHOSPHATE
ATP = ADENOSINE TRIPHOSPHATE

GDP = GUANOSINE DIPHOSPHATE
cAMP = CYCLIC ADENOSINE MONOPHOSPHATE

[R] = HORMONE RECEPTOR
  s = STIMULATORY i = INHIBITORY

(G) = GUANINE NUCLEOTIDE-BINDING PROTEIN
  s = STIMULATORY   i = INHIBITORY
  α = α SUBUNIT β = β SUBUNIT

(C) = ADENYLATE CYCLASE

___(+)___ = STIMULATION

----(-)---- = INHIBITION

Figure 27

- 49 -
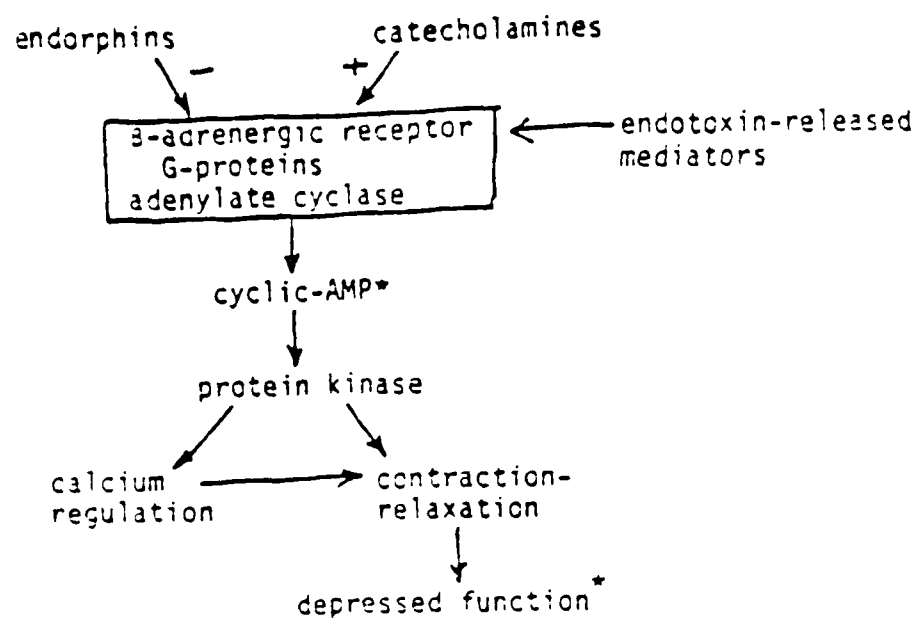
Figure 48

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